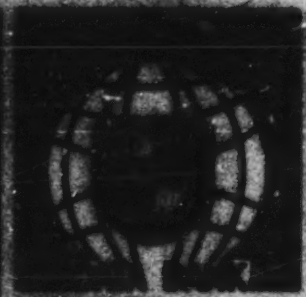


ONCOLOGY OVERVIEW**COMPLETE
ORIGINAL****SELECTED ABSTRACTS****ON****INTEGRATED
VIRAL GENOMES****FEBRUARY 20, 1979**

**U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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INTRODUCTION

This ONCOLOGY OVERVIEW on integrated viral genomes covers the publication years from 1973 to the recent entries in the CANCERLINE data base. The strategy used for the on-line data base search is available upon request from the CIDAC office and can be entered at any MEDLARS/MEDLINE terminal system in order to obtain continuing updates in this area.

The scope of this OVERVIEW covers the variety of techniques used to rigorously identify and localize the integrated genome. The abstracts are organized by virus grouping, and within each grouping, according to the techniques used for the detection and characterization of the integrated genome.

This OVERVIEW was prepared by Robert A. Weinberg, MIT Center for Cancer Research and Barbara E. Hindman of the CIDAC for Virology, Immunology and Biology, The Franklin Institute Research Laboratories.

EDITORIAL COMMENTARY

Integrated viral genomes have been studied intensively since the initial observations of Sambrook, Westphal, Srinivasan and Dulbecco (1968) concerning the association of SV40 genome with the cellular DNA of the virus-transformed mouse cell. Their demonstration of an alkali-stable linkage between the viral and cellular genome established a rigorous definition of the integrated state. Only a direct proof of the covalent linkage of viral and cellular genomes could thereafter be considered a rigorous demonstration of viral integration.

This demonstration of an integrated SV40 genome generated a premature conclusion by some investigators - that integration and viral transformation are inseparable, mechanistically related processes. However, it has since become clear that the Epstein-Barr genome is able to perpetuate itself in a plasmid state. Analogously, the abortive transformation induced by some papovaviruses may well be controlled by unintegrated viral genomes. In these instances, neither of which is fully characterized presently, the ability to induce transformation appears to be dissociated from integration. Conversely, many retrovirus genomes (e.g. leukemia, leukosis viruses) are integrated into fibroblast chromosomes without producing visible transformation. Of some interest is the recent preliminary report that the non-oncogenic adeno-associated virus may occasionally perpetuate its genome as an integrated provirus (Handa, Shiroki, and Shimojo, 1977). These examples only indicate that integration is a state which oncogenic genomes will frequently but not inevitably choose, and that integration itself does not imply oncogenic transformation.

The continued presence of the viral genome is required in many virus-transformed cell lines in order to ensure a stabilization of the transformed state. This is most directly indicated by use of viral mutants whose genomes specify a thermolabile transforming factor. Such cell lines show a transformed phenotype at a low, permissive temperature but revert to a relatively normal phenotype at a temperature which is non-permissive for the viral factor. The necessity of the continued presence of a viral protein for maintenance of the transformed state implies a requirement for continued presence of a functional viral gene.

Selection of a transformed cell clone therefore imposes two independent requirements on the viral genome which initiates the transformation:

1. that the genome be able to specify a transforming factor with the potency and specificity required for induction of the transformed phenotype; and
2. that the genome be able to perpetuate itself in all of the descendants of the initially transformed cell.

Viewed in this light, integration is the simplest response to the second requirement since the viral genome becomes automatically co-replicated with that of the host cell. The alternative to integration is maintenance of the viral genome in a plasmid state, a physiologically complex process which demands a coordinate, yet independent replication of host and viral genomes over many generations.

Three groups of oncogenic viruses - adeno-, papova, and retroviruses - yield transformed cell lines containing integrated viral genomes (evidence concerning physical state of the herpes genome in most transformed cells is still lacking). The finding of integrated genomes of papova- and adenovirus-transformed cells has led to the assumption by some that integration is a normal step in the growth cycle of these viruses. In fact, only retroviruses appear to integrate their genomes, as a necessary step in their replication. There is no shred of evidence that papovaviruses, adenoviruses and herpesviruses utilize integrated genomes as necessary participants in replication in their normal permissive host cells. Comparison of plaque to focus-forming titers of these viruses indicated that establishment of a functional, integrated viral genome or sub-genomic fragment is a low frequency, perhaps accidental occurrence. The sensitive procedures for the selection and isolation of transformed foci have made these rare events quantifiable and the transformed cell a much studied object of laboratory investigation.

The undirected nature of the papovavirus integration is illustrated most vividly by the studies of Botchan, Topp and Sambrook (1976). Their work indicates that there are no specific sites on the host chromosome used for insertion of the viral genome. Furthermore, the circular viral genome appears to be broken at any of a number of possible sites during the linearization of the genome which accompanies integration. Only fragments of the viral genome may be integrated. An analogous picture is emerging for adenovirus. The structure of the integrated papova genome is most suggestive of a type of illegitimate recombination between fragments of the viral genome and regions of cellular chromosomes which perchance became accessible after infection by the virus. Most integrating events by fragments of the SV40 genome may not lead to transformation, either because the improper portion of the viral genome is integrated, or because the genome is integrated in a configuration or chromosomal environment which does not allow its transcription into functional viral mRNA.

Retroviruses appear to be distinctly different. It is already clear that the viral genome exists in the integrated state in virtually all productive infections and that this integrated provirus is the major, if not sole, possible template for synthesis of progeny viral RNA. The absence of unintegrated DNA from many productively infected cell lines indicates strongly the nonessential nature of the unintegrated material in maintaining the infection. The seemingly obligate role of the integrated retrovirus genome would suggest a specific mechanism of integration in analogy with the integration of the lambda bacteriophage genome, but few data exist yet on this point.

The existence of integrated transforming genomes has led some to postulate that transformation is achieved by insertion of viral DNA into critical regions of the cellular chromosome. However, if transformation is generally seen to be maintained by a viral-coded protein, as discussed above, then the chromosomal location of the integrated genome may be of secondary importance in that certain chromosomal integration sites may allow or disallow efficient transcription of the viral DNA.

The detailed characterization of the structure of the integrated genome will very likely be achieved via the Southern gel-filter blotting technique, initial exploitation of which is cited in several papers here.

The resolving power and sensitivity of this technique should permit exact quantitation of the integration genomes and eventually yield important information on the mechanisms of integration and the chromosomal sites at which integration occurs.

REFERENCES

1. The Integrated Viral DNA in SV40 Transformed Cells. Sambrook, Westphal, Srinivasan and Dulbecco. PNAS, Vol. 60, 1288-1295, 1968.
2. Establishment and Characterization of KB Cells Latently Infected with Adeno Associated Virus Type 1. Handa, Shiroki and Shimojo. Virology, Vol. 82, 84-92, 1977.
3. The Arrangement of Simian Virus 40 Sequences: The DNA of Transformed Cells. Botchan, Topp and Sambrook. Cells, Vol. 9, 269-287, 1976.

I. APPROACHES FOR THE STUDY OF INTEGRATED RETROVIRUS GENOMES

A. Retroviruses: Isolation of Integrated Genomes in Alkaline Sucrose Gradients

I. USE OF ALKALINE SUCROSE GRADIENTS IN A ZONAL ROTOR TO DETECT INTEGRATED AND UNINTEGRATED AVIAN SARCOMA VIRUS-SPECIFIC DNA IN CELLS.

Varmus HE, Heasley S, Linn J, Wheeler K
Dept. Microbiology, Univ. California, San Francisco, CA 94143

J Virol; 18(2):574-585 1976

Integrated and unintegrated forms of avian sarcoma virus-specific DNA in cells were distinguished by sedimentation through an alkaline sucrose gradient in a slowly reorienting zonal rotor. The cell types were chick cells that inherit viral genes, virally transformed but non-permissive mammalian cells, transformed virus-producing avian cells, and acutely infected avian cells. Most, if not all, viral DNA appeared completely integrated into the host cell genome in an avian sarcoma virus-transformed mammalian cell and in normal chicken cells (in which viral DNA is genetically transmitted). Fully transformed duck cells and duck embryo fibroblasts infected for 20 to 72 hr contained both integrated and unintegrated viral DNA; up to one copy per cell was integrated within 20 hr after infection, and four to eight copies were integrated in fully transformed cells. The amount of unintegrated DNA varied but it comprised over 75% of the viral DNA in acutely infected cells and from 20% to 70% of the viral DNA in fully transformed cells. The unintegrated DNA in either case consisted principally of duplexes with "minus" strands the length of a subunit of the viral genome (2.5×10^6 to 3×10^6 daltons) and relatively short "plus" strands (0.5×10^6 to 1.0×10^6 daltons).

2. SYNTHESIS OF AVIAN ONCORNAVIRUS DNA IN INFECTED CHICKEN CELLS.

Ali M, Baluda MA
U. California, Sch. Med., Los Angeles
J Virol; 13(5):1005-1013 1974

The intracellular synthesis and integration of viral DNA (vDNA) into the host cell genome was studied in cultured chicken embryo fibroblasts infected with avian sarcoma or leukemia viruses. The newly synthesized vDNA was detected by hybridization with 70S viral RNA. Extraction of infected cell DNA by the selective procedure of Hirt resulted in the enrichment of newly synthesized vDNA in the low-molecular weight supernatant fraction, leaving the bulk of the cellular DNA containing integrated vDNA in the high-molecular weight pellet fraction. This approach led to the detection of intracellular vDNA synthesis within 1 hr after infection and to the detection of vDNA integration into the cellular DNA within 24 hr. There was a several-fold increase in the vDNA content of the infected cells during the initial phase of virus infection. However, only a portion of this newly synthesized vDNA appeared to become covalently linked with the high-molecular weight cellular DNA. Most of the remaining unintegrated vDNA gradually disappeared. The sedimentation profiles of minimally sheared cellular DNA in

alkaline sucrose velocity gradients suggest that vDNA is synthesized as free linear molecules of approximately 3×10^6 daltons; these are subsequently covalently linked to the host cell DNA.

3. SYNTHESIS AND INTEGRATION OF VIRAL DNA IN CHICKEN CELLS AT DIFFERENT TIMES AFTER INFECTION WITH VARIOUS MULTIPLICITIES OF AVIAN ONCORNAVIRUS.

Khoury AT, Hanafusa H
Rockefeller Univ., New York, NY 10021
J Virol; 18(2):383-400 1976

In the attempt to find out if integration of the provirus resulting from RNA tumor virus infection is limited to specific sites in cell DNA, the variation in the number of virus-specific DNA copies produced and integrated in chicken embryo fibroblasts was determined at long and short intervals after high- and low-multiplicity Rous-associated virus 3 (RAV-2) infections and after several transfers. The number of copies of viral DNA in cells was determined by initial hybridization kinetics of single-stranded viral complementary DNA with a moderate excess of cell DNA. This hybridization accounted for the different sizes of cell DNA and complementary DNA in the hybridization mixture. Uninfected chicken embryo fibroblasts have approximately seven copies per haploid genome of DNA sequences homologous to part of the RAV-2 genome. Infection with RAV-2 added additional copies and different sequences of RAV-2-specific DNA. Between 13 and 20 hr after infection, there were 3-10 additional copies per haploid genome; this number remained constant despite increased multiplicity infection. Between 20 and 40 hr postinfection, after some of the additional viral DNA was integrated, the cells accumulated up to 100 copies. Most of these copies were unintegrated. This number decreased with cell transfer, until cells were left with one to three copies of additional viral DNA sequences per haploid genome, of which most were integrated. The finding that viral infection caused the permanent addition of 1-3 copies of integrated viral DNA, despite the cells being confronted with up to 100 copies per haploid genome after infection, is consistent with a hypothesis that chicken cells contain a limited number of specific integration sites for the oncornavirus genome.

B. Retroviruses: Isolation of Integrated Genomes Linked with Repeated Cellular Sequences - Network Formation

4. SYNTHESIS AND INTEGRATION OF ROUS SARCOMA VIRUS PROVIRAL DNA IN DUCK EMBRYO FIBROBLAST CELLS. (PP. 315-323)

Guntaka RV, Bishop JM, Varmus HE
Fundamental Aspects of Neoplasia. Waksman Institute of Microbiology of Rutgers University, New York, 424 pp., 1975.

Results of studies on the synthesis and characteristics of proviral DNA (pDNA) and the effect of ethidium bromide (EB) on integration of pDNA into host cell DNA are summarized. Using molecular hybridization, viral DNA can be detected in the cytoplasm of duck cells infected with the B77 strain of Rous sarcoma virus 3-6 hr following infection, but 9 hr after infection, most of the pDNA is localized in the nucleus. The size of the pDNA in the cytoplasm of infected

cells was determined by centrifugation of DNA from cytoplasmic extracts in both neutral and alkaline sucrose gradients. Proviral DNA was assayed by annealing each fraction with labeled complementary cDNA synthesized *in vitro*. These experiments indicated that pDNA is a duplex with a MW of $6 \text{ to } 7 \times 10^6$ daltons and that some of the pDNA is present in a closed circular form. Duck cells were pretreated with EB for 4 hr and then infected with B77 virus in the presence of the dye for 40 hr. High molecular weight DNA was isolated and assayed for integration by the network test. Under these conditions, there is no decrease in the amount of pDNA made, but the extent of integration was reduced by a factor of at least 5. Virus production, measured either by incorporation of ^3H -uridine into particles banding at 1.15-1.17 g/ml in an equilibrium sucrose gradient or by focus formation, is proportionately diminished. Virus-specific RNA is also proportionately decreased in the presence of EB. These results suggest that virus production and cellular transformation depend upon integration of the provirus into cell DNA. The mechanism of inhibition of integration by EB is unknown, but it is speculated that EB binds to newly synthesized pDNA and interferes with the process of circularization, since at least some pDNA probably exists in a circular form before integration. (18 refs)

5. INTEGRATION OF DEOXYRIBONUCLEIC ACID SPECIFIC FOR ROUS SARCOMA VIRUS AFTER INFECTION OF PERMISSIVE AND NONPERMISSIVE HOSTS (MEETING ABSTRACT).

Varmus HE, Vogt PK, Bishop JM
Dept. Microbiol., U. California, San Francisco
Proc Natl Acad Sci USA; 70(11):3067-3071 1973

A relatively simple, efficient, and stringent technique for studying the integration of DNA and RNA tumor virus genomes is presented. The technique involves testing the DNA in networks for virus-specific nucleotide sequences by molecular hybridization. The finding of virus-specific DNA in networks demonstrates covalent linkage of viral DNA to strands of cell DNA containing repeated sequences, and thus its integration into the host genome. This approach was used to study Rous sarcoma virus (RSV)-specific DNA in duck embryo fibroblasts and mammalian cells, particularly BALB/c 3T3 cells, following infection by RSV. In both cell types, neither of which normally contains nucleotide sequences specific for RSV, transformation by the virus resulted in the appearance of RSV-specific DNA, which was covalently integrated into strands of host-cell DNA containing reiterated sequences. The viral DNA appeared in the cells soon after infection, presumably as a product of the intracellular activity of virus-associated RNA-directed DNA polymerase. The assay therefore constitutes an assay for *in vivo* polymerase activity and may permit detailed analysis of the mechanism of RNA-directed DNA synthesis in the host cell. A potential limitation of the technique resides in the possibility that viral DNA might be integrated specifically into an uncommon region of the cell DNA that is devoid of reiterated sequences and does not form networks; in this case, integrated viral DNA would not be present in the networks. It is concluded that the genomes of both RNA and DNA tumor viruses are integrated into host-cell DNA, although the sites and mechanism for integration are unknown.

6. THE PERSISTENCE AND EXPRESSION OF VIRUS-SPECIFIC DNA IN REVERTANTS OF ROUS SARCOMA VIRUS-TRANSFORMED BHK-21 CELLS.

Deng CT, Boettiger D, MacPherson I, Varmus HE
Dept. Microbiol., Univ. California, San Francisco
Virology; 62(2):512-521 1974

Clones of Rous sarcoma virus-transformed baby hamster kidney cells and subclones reverted to normal phenotype were

found to contain one copy of integrated virus-specific DNA/diploid cell. In the transformed clones, virus-specific DNA was transcribed into RNA at low levels similar to those observed in other nonpermissive RSV-transformed cells. Virus-specific RNA concentrations were still lower in the revertant clones. The amount of virus-specific RNA in these clones correlated with the frequency with which Rous sarcoma virus could be rescued after fusion with chick embryo cells. Treatment of a revertant clone with 5-bromodeoxyuridine (25 microg/ml) increased the concentration of viral RNA and the frequency of rescue. These results suggest that control of viral gene expression in reverted cells is at least partially regulated at the transcriptional level.

7. ETHIDIUM BROMIDE INHIBITS APPEARANCE OF CLOSED CIRCULAR VIRAL DNA AND INTEGRATION OF VIRUS-SPECIFIC DNA IN DUCK CELLS INFECTED BY AVIAN SARCOMA VIRUS.

Guntaka RV, Mahy BW, Bishop JM, Varmus HE
Dept. Microbiol., Univ. California, San Francisco
Nature (Lond); 253(5492):507-511 1975

The inhibitory effect of ethidium bromide (EB) on the integration of avian sarcoma virus DNA into the genome of Peking duck cells is reported. When ducks were pretreated 6 hr with EB (1.0 ug/ml) then infected by B77 avian sarcoma virus, it was found that the drug did not inhibit the synthesis of viral DNA, i.e. did not inhibit reverse transcriptase *in vivo*. However, network DNA from cells infected in the absence of EB showed accelerated rate of reassociation of labeled viral DNA by a factor of 5, whereas that from EB treated cells had only a marginal influence on the reassociation, indicating that less than 15% viral DNA was integrated into the host genome. Commensurate enrichment of EB treated supernatant with viral specific sequences confirmed the finding. Conc'n of EB above 1.0 ug/ml suppressed synthesis of viral DNA. EB was found to suppress formation of closed circular DNA by a factor of 4 to 5 without affecting other forms, indicating that its integration inhibitory effect may be due to intercalation within double-stranded viral DNA, preventing or reversing the formation of supercoiled DNA. EB (1.0 ug/ml) was found to inhibit integration and virus production, further substantiating the conclusion that virus production depends on integration of the viral DNA. A scheme for virus production is proposed. (20 refs)

C. Retroviruses: Nucleic Acid Hybridization Kinetics for the Quantitation and Localization of Proviruses

8. DETECTION OF AVIAN TUMOR VIRUS-SPECIFIC NUCLEOTIDE SEQUENCES IN AVIAN CELL DNAs (MEETING ABSTRACT).

Varmus HE, Weiss RA, Friis RR, Levinson W, Bishop JM
U. California, Sch. Med., San Francisco
Proc Natl Acad Sci USA; 69(1):20-24 1972

The effect of chick embryo DNA on reassociation kinetics of labeled double-stranded DNA produced by RNA-dependent DNA polymerase from Rous sarcoma virus (RSV) was used to measure virus-specific nucleotide sequences in normal and transformed cells. Fifty percent reassociation (half-Cot) values indicated the presence of multiple copies of viral nucleotide sequences in DNA from normal chick embryos, RS-induced chicken wing sarcomas and *in vitro* RSV-transformed cells. Multiple copies were also detected in DNA from cells harboring Rous associated virus (RAV-O) and in cells positive for viral group-specific antigen (gs+); they were not present in HeLa cells or salmon-sperm DNA. There were no significant differences between viral nucleotide sequences in transformed and untransformed cells or between sequences in gs+ and gs- cells. Quail embryo cells, which were not gs+ and

lacked RAV-O, also contained nucleotide sequences homologous to RSV, DNA and RAV-O DNA. The results suggest that viral genes may be present in normal cells.

9. INTEGRATED STATE OF ONCORNAVIRUS DNA IN NORMAL CHICKEN CELLS AND IN CELLS TRANSFORMED BY AVIAN MYELOBLASTOSIS VIRUS.

Markham PD, Baluda MA
U. California Sch. Med., Los Angeles
J Virol; 12(4):721-732 1973

The covalent linkage of oncornavirus-specific DNA to chicken DNA was investigated in normal chicken embryo fibroblasts (CEF) and in virus-producing leukemic cells transformed by avian myeloblastosis virus (AMV). The virus-specific sequences present in cellular DNA fractionated by different methods were detected by DNA-RNA hybridization by using 70S AMV RNA as a probe. In CEF and in leukemic cells, the viral DNA appeared to be present only in the nucleus. After cesium chloride-ethidium bromide density equilibrium sedimentation, the viral DNA was present as linear, double-stranded molecules not separable from linear chicken DNA. After extraction by the Hirt procedure, the viral DNA precipitated with the high-molecular-wt DNA. After alkaline sucrose velocity sedimentation, the viral DNA cosedimented with the high-molecular-wt cellular DNA. The results indicate that in both types of cells studied, the oncornavirus-specific DNA sequences were covalently linked by alkali stable bonds to nuclear cellular DNA of high molecular wt and were not present in free form of any size.

10. STUDIES ON CHARACTERIZATION OF THE INTEGRATION SITES OF AVIAN RNA TUMOR VIRUS-SPECIFIC DNA. (PP. 1005-1007)

Evans RM, Shoyab M, Baluda MA
Tumor Viruses Cold Spring Harbor Symposia on
Quantitative Biology. vol. 39, Cold Spring Harbor Lab.
(Cold Spring Harbor, NY): vol 39, 1975

In investigation of the host sequences adjacent to integrated viral DNA, it was found that endogenous viral sequences in normal cells appeared to be associated with cell sequences reiterated 1,200 times and that each integration is approximately equal to one 35S RNA subunit. In avian myeloblastosis virus (AMV)-infected cells, the additional AMV-specific DNA sequences reassociated as if they were integrated adjacent to unique cellular DNA or in tandem with the endogenous viral DNA sequences.

11. INTEGRATION OF PROVIRAL DNA IN CHICKEN CELLS INFECTED WITH SCHMIDT-RUPPIN ROUS SARCOMA VIRUS IS NOT ENHANCED BY DNA REPAIR.

Tsuruo T, Baluda MA
Dept. Pathology, UCLA Sch. Medicine, Los Angeles, CA
90024
J Virol; 23(3):533-542 1977

The effect DNA repair might have on the integration of exogenous proviral DNA into host cell DNA was investigated by comparing the efficiency of proviral DNA integration in normal chicken embryonic fibroblasts and in chicken embryonic fibroblasts treated with UV or 4-nitroquinoline-1-oxide. The cells were treated with UV or 4-nitroquinoline-1-oxide at various time intervals ranging from 6 hr before to 24 hr after infection with Schmidt-Ruppin strain A of Rous sarcoma virus. The chicken embryonic fibroblasts were subsequently cultured for 18 to 21 days to ensure maximum integration and elimination of nonintegrated exogenous proviral DNA before DNA was extracted. Integration of proviral DNA into the cellular genome was quantitated by hybridization of denatured cellular DNA on filters with an excess

of H³-labeled 35S viral RNA. The copy number of the integrated proviruses in normal cells and in infected cells was also determined from the kinetics of liquid RNA-DNA hybridization in DNA excess. Both RNA excess and DNA excess methods of hybridization indicate that two to three copies of the endogenous provirus appear to be present per haploid normal chicken cell genome and that two to three copies of the provirus of Schmidt-Ruppin strain A of Rous sarcoma virus become integrated per haploid cell genome after infection. The copy number of viral genome equivalents integrated per cell treated with UV or 4-nitroquinoline-1-oxide at different time intervals before or after infection did not differ from the copy number in untreated but infected cells. This finding supports our previous report that the integration of oncornavirus proviral DNA is restricted to specific sites in the host cell DNA and suggests a specific mechanism for integration. (Author abstract) (56 Refs)

12. DETECTION OF AVIAN TUMOR VIRUS RNA IN UNINFECTED CHICKEN EMBRYO CELLS.

Hayward WS, Hanafusa H
Public Hlth. Res. Inst. City New York, N.Y.
J Virol; 11(2):157-167 1973

Uninfected chicken embryo cells were analyzed for the presence of viral ribonucleic acid (RNA) by molecular hybridization with the single-stranded deoxyribonucleic acid (DNA) product of the RNA-dependent DNA polymerase contained in avian sarcomaleukosis virions. Viral RNA was detected in all cells which contained the avian tumor virus group-specific antigen and the virus-related helper factor. The amounts of viral RNA in these cells ranged from approximately 3 to 40 copies of viral-specific sequences per cell. In general, the viral RNA content correlated with the level of helper activity in the cells. Cells infected with Rous-associated virus 2 contained 3,000 to 4,000 copies of viral RNA per cell. RNA from these infected cells hybridized with nearly 100% of the viral 3H-DNA. By contrast, a maximum of less than 50% hybridization was obtained with RNA from the uninfected helper-positive cells, suggesting that not all of the viral RNA sequences were present in these cells. No viral RNA was detected in cells which lacked group-specific antigen and helper activity. Under the conditions used in these studies, less than 0.3 viral genome equivalents of RNA per cell would have been detected.

13. DETECTION AND ENUMERATION OF TRANSFORMATION-DEFECTIVE STRAINS OF AVIAN SARCOMA VIRUS WITH MOLECULAR HYBRIDIZATION.

Stehelin D, Fujita DJ, Padgett T, Varmus HE, Bishop JM
Dept. Microbiology, Univ. California, San Francisco, CA
94143
Virology; 76(2):676-684 1977

Propagation of avian sarcoma viruses (ASV) leads to the formation of genetic variants that cannot induce sarcomas or transform fibroblasts in culture. Such transformation-defective (td) strains are deletion mutants that lack 10%-20% of the genetic information of the parent virus. To study these td strains, single-stranded DNA (cDNA-sarc) complementary to the nucleotide sequences deleted from the genome of ASV during the genesis of td variants was prepared. cDNA-sarc can hybridize to genome RNA from any strain of ASV, but it cannot react with RNA from td variants, and this specificity was incorporated in an assay for td virus, that permits the rapid and accurate enumeration of td deletions. The process can also be applied to deletions in other viral genes. All 20 copies of the proviral DNA for ASV in XC cells were shown to contain src (the viral gene for the maintenance of cellular transformation by ASV). It was also shown that single avian

cells can contain functioning proviruses for both ASV and a congenic deletion mutant. Available evidence suggests that the deletion of *src* arises during the synthesis or integration of proviral DNA, not during transcription of viral RNA from provirus. (21 Refs)

14. CHARACTERIZATION OF MURINE LEUKAEMIA VIRUS-SPECIFIC DNA PRESENT IN NORMAL MOUSE CELLS.

Gelb LD, Milstien JB, Martin MA, Aaronson SA
Lab. Biology of Viruses, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD 20014
Nature: 244(133):76-79 1973

The minor component of labeled, double stranded (ds) Kirsten murine leukemia virus (KiMuLV)-specific DNA, which appears to contain genetic information present in 70Svedberg (S) RNA, was isolated, characterized and used to detect homologous virus-specific DNA sequences in mouse cells. In addition, the high mol wt fraction of normal cellular DNA was examined for virus-specific DNA sequences to determine whether type C viral information is an integral part of the mouse cell genome. Single-stranded, in vitro virus-specific DNA (slowly reassociating fraction) reannealed with a C0t1/2 (product of the DNA concentration (C0) and the time (t) taken for 50% of the DNA sequences to reassociate, expressed as moles of nucleotide x sec/liter) of 1.1 to 1.7×10^{10} -2 mole sec/liter. Simian virus 40 DNA reassociated with a C0t1/2 of 2.0×10^{10} -3 mole sec/liter suggesting that the slowly reassociating fraction of KiMuLV had a genome complexity equivalent to 1.6 to 2.5×10^7 and a mol wt corresponding to RNA sedimenting at 70S. The ds DNA product of KiMuLV conferred RNase resistance on 70% of the 70S viral RNA following a 1-wk incubation in 50% formamide. The reannealing of H3-KiMuLV ds DNA was significantly increased by mouse cellular DNA but not by DNAs of other species. The results indicate the presence of mouse type C virus-specific DNA (10 to 14 equivalents per diploid cell) in normal mouse cells. All the viral DNA equivalents present in total cellular DNA were detected in the high mol wt fraction indicating that the MuLV-specific DNA was covalently linked to the cellular DNA. (16 Refs)

15. PARTIAL TRANSCRIPTION OF MURINE TYPE C VIRAL GENOMES IN BALB/C CELL LINES.

Benveniste RE, Todaro GT, Scolnick EM, Parks WP
Natl. Cancer Inst., Bethesda, Md.
J Virol: 12(4):711-720 1973

The mouse cell line BALB/c 3T3 and its derivatives transformed spontaneously or by treatment with a variety of external agents were analyzed for cytoplasmic RNA complementary to DNA products prepared from the Kirsten strain of murine sarcoma-leukemia virus, and from an endogenous type C virus of BALB/c 3T3. Although none of these cell lines spontaneously releases complete type C virions, they all contain RNA which is partially homologous to a portion of the 35S RNA isolated from these viruses. The parental cell line, BALB/c 3T3, contains a low level of viral-related RNA, and there is an increased amount of this RNA in some of the transformed cells. The RNA detected represents only a fraction of the viral RNA found in virus-producing cells. The formation of RNA:DNA hybrids was detected by equilibrium centrifugation in Cs₂SO₄ density gradients and by analysis with a single-strand-specific nuclease from *Aspergillus oryzae*. Viral DNA products prepared from an endogenous reaction with whole virus in the presence of actinomycin D or from purified 70S viral RNA as template using avian myeloblastosis virus DNA polymerase yield comparable data. In addition, all of the BALB/c lines examined produce detectable levels of murine type C virus group-specific antigens.

16. EVIDENCE THAT THE AKR MURINE-LEUKEMIA-VIRUS GENOME IS COMPLETE IN DNA OF THE HIGH-VIRUS AKR MOUSE AND INCOMPLETE IN THE DNA OF THE "VIRUS-NEGATIVE" NIH MOUSE (MEETING ABSTRACT).

Chattopadhyay SK, Lowy DR, Teich NM, Levine AS, Rowe WP

Natl. Cancer Inst., Bethesda, Md.

Proc Natl Acad Sci USA: 71(1):169-171 1974

The AKR mouse has a high titer of murine leukemia virus early in life, and virus-negative cells derived from embryos of this mouse strain can be activated to yield murine leukemia virus by treatment with 5-iododeoxyuridine. In contrast, the NIH Swiss mouse has a low leukemia incidence and no murine leukemia virus has been isolated from it (virus-negative). The difference between AKR and NIH mice has been investigated by examining the sequences specific for murine leukemia virus in nucleic acids of these mice. A single-stranded viral-DNA probe synthesized in vitro using murine-leukemia-virus from the AKR mouse contains at least 87% of the sequences present in the 70S viral RNA; most of these sequences are in proportions similar to their content in the 70S RNA. Using this probe in nucleic acid hybridization experiments, it was shown that NIH-mouse-cell DNA and AKR-mouse-cell DNA differ with respect to sequences specific for AKR murine-leukemic-virus: NIH mouse-cell DNA lacks some of the virus-specific sequences present in AKR-mouse-cell DNA, and there are two distinct sets of virus-specific sequences in AKR-mouse-cell DNA. RNA from virus-negative AKR-mouse cells grown in tissue culture contain some, but not all, virus-specific RNA sequences; however, within 48 hr after initiating treating of these cells with 5-iododeoxyuridine, the complete viral genome is represented in cellular RNA.

17. DIFFERENCES BETWEEN THE INTEGRATION OF AVIAN MYELOBLASTOSIS VIRUS DNA IN LEUKEMIC CELLS AND OF ENDOGENOUS VIRAL DNA IN NORMAL CHICKEN CELLS.

Evans RM, Baluda MA, Shoyab M

Univ. California Sch. Medicine, Dept. Microbiology and Immunology, Los Angeles, CA 90024

Proc Natl Acad Sci USA: 71(8):3152-3156 1974

The nature of integrated avian myeloblastosis virus (AMV) DNA in normal and leukemic chicken cells was studied by sequential nucleic acid hybridization procedures which localized the viral-specific DNA in cellular DNA regions differing in reiteration frequency. DNA was isolated from normal or leukemic cells, fragmented, and the fragments denatured and fractionated on hydroxyapatite according to their reassociation rates. The concentration of the viral DNA sequences present in each single-stranded DNA fraction was determined by nitrocellulose filter immobilization and hybridization in the presence of 3H-70Svedberg (S) AMV RNA. Large fragments of DNA were used to determine the effect of adjacent cellular DNA sequences on the reassociation kinetics of viral DNA sequences. In normal cells, the endogenous viral sequences were integrated adjacent to reiterated cell DNA. Each integrated proviral unit was approx equivalent to the 35S RNA subunit of the virion. Second order kinetics of the renaturation in normal cells suggested that the reiterated cellular sequences covalently linked to viral DNA belonged to a family of sequences that renatured at a C0t1/2 (product of the DNA concentration (C0) and the time (t) taken for 50% of the DNA sequences to reassociate, expressed as moles of nucleotide x sec/liter) of 0.28 mole sec/liter and corresponded to a reiteration frequency of 1,200. In the infected cells, additional viral sequences were observed which appeared to integrate as single 35S subunits adjacent to unique cellular DNA sequences or as multiple 35S subunits end-to-end. (25 Refs)

18. INFECTION OF PREIMPLANTATION MOUSE EMBRYOS AND OF NEWBORN MICE WITH LEUKEMIA VIRUS: TISSUE DISTRIBUTION OF VIRAL DNA AND RNA AND LEUKEMOGENESIS IN THE ADULT ANIMAL.

Jaenisch R, Fan H, Croker B

The Salk Institute for Biological Studies, Post Office Box 1809, San Diego, California 92112

Proc Natl Acad Sci USA; 72(10):4008-4012 1975

Explant mouse embryos derived from low leukemia incidence strains were infected with Moloney murine leukemia virus (M-MuLV) at the 4-8 cell stage of development. After cultivation in vitro to the blastocyst stage, the embryos were surgically transferred to the uteri of pseudopregnant surrogate mothers. Of 15 animals born, one developed a leukemia at 8 weeks of age. When autopsied, this leukemia was found to be the lymphatic type, as is typical for the M-MuLV-induced disease. In addition, infectious M-MuLV virus was isolated from the serum. Molecular hybridization tests for the presence of M-MuLV-specific sequences were conducted on DNA and RNA extracted from eight different organs. The DNA/DNA reannealing experiments revealed the presence of two classes of M-MuLV-specific sequences in equal concentrations in all tissues tested. The less abundant class of M-MuLV-specific sequences was not detected in tissues from uninfected animals or in non-target tissues of leukemic animals infected at birth. The results are consistent with the working hypothesis that the virus was integrated in all cells of the animal, possibly including the germ line. Fifty to 100 times more M-MuLV-specific RNA was detected in tumor tissues than was found in non-target organs such as liver, brain, and testes. Since all organs contained the same amount of virus-specific DNA, these results indicate that the M-MuLV-specific DNA can be differentially expressed in different tissues. (Author Abstract)

19. SITES OF INTEGRATION OF AVIAN ONCORNAVIRUSES IN HOMOLOGOUS AND HETEROLOGOUS HOSTS.

Dastoor MN

Univ. California, Los Angeles, CA

Diss Abstr Int B; 37(5): 2072B 1976

The integration site of avian myeloblastosis virus (AMV) proviral DNA in DNA from leukemic chicken myeloblasts was investigated. The AMV appeared to be integrated in tandem with the endogenous proviral DNA with contiguous cellular sequences, which appeared to be repeated approx 1,200 times/haploid genome. It appeared that the integration of AMV provirus was site specific and restricted in number. The integration of avian oncornaviruses in the genomes of heterologous hosts was investigated by defining the repetitive frequency of the host DNA at which the proviral DNA integrates. The results indicate that both avian sarcoma virus (B-77) as well as the leukosis virus (RAV-61) integrate in the unique region of duck embryonic DNA. B-77 proviral DNA was found associated with repeated host DNA in the transformed mouse 3T3 cells. (0 Refs)

20. EVIDENCE FOR TANDEM INTEGRATION OF AVIAN MYELOBLASTOSIS VIRUS DNA WITH ENDOGENOUS PROVIRUS IN LEUKEMIC CHICKEN CELLS.

Shoyab M, Dastoor MN, Baluda MA

Dept. Microbiology and Immunology, Univ. California at Los Angeles Sch. Medicine, Los Angeles, CA 90024

Proc Natl Acad Sci USA; 73(5):1749-1753 1976

The integration site of avian myeloblastosis virus (AMV) proviral DNA in DNA from leukemic chicken myeloblasts was studied by three sequential nucleic acid hybridizations.

Large denatured cellular DNA fragments (2.1×10^6 daltons) were reassociated and fractionated according to sequence reiteration frequency. Next, the DNA remaining single-stranded in each fraction was immobilized on nitrocellulose filters and hybridized with an excess of unlabeled 70S RNA from Rous-associated virus-0 to saturate the endogenous proviral DNA sequences. Finally, the filter-immobilized DNA was hybridized with ^3H -35S RNA from AMV to quantitate the AMV-specific DNA in each fraction. The AMV provirus in AMV-induced leukemic myeloblasts appeared to be integrated in tandem with the endogenous proviral DNA and with contiguous cellular sequences that repeat approx 1,200 times per haploid cell genome. Each provirus integration unit in single-stranded leukemic cell DNA was equivalent to two 35S viral RNA subunits (total 6×10^6 daltons). It is suggested that the integration of AMV provirus is site-specific and occurs at a restricted number of sites (one to two per chicken cell haploid genome). (37 refs)

21. QUANTITATIVE STUDIES OF INTEGRATION OF MURINE LEUKEMIA VIRUS AFTER EXOGENOUS INFECTION.

Chattopadhyay SK, Rowe WP, Levine AS

Section on Infectious Diseases, Pediatric Oncology Branch, National Cancer Institute, Bethesda, MD 20014 MD 20014

Proc Natl Acad Sci USA; 73(11):4095-4099 1976

Using a (^3H)DNA probe prepared from AKR murine leukemia virus, we determined the number of copies of the AKR virus genome integrated into the cellular DNA after exogenous infection of NIH mouse, AKR mouse, and rat cells in tissue culture. NIH mouse cells, which lack a portion of the viral genome (referred to as Gross-AKR specific sequences), incorporated three to four copies of these sequences per haploid genome. AKR cells, in which the Gross-AKR specific sequences are already present as three to four copies per haploid genome, did not show any distinct change in copy number after infection. Rat cells, which lack DNA sequences homologous to murine leukemia virus, incorporated one copy of the viral genome per haploid genome. It is inferred that the presence of viral sequences may affect the efficiency of integration of exogenous provirus, and that there may be a limit to the number of copies that can be inserted. (Author Abstract)

22. PROVIRAL SEQUENCES IN SPLEEN OF A GIBBON WITH SPONTANEOUS LYMPHOMA (MEETING ABSTRACT).

Wong-Staal F, Gallo RC, Sarngadharan MG, Gillespie D

National Institutes of Health, Bethesda, Md 20014

Proc Am Assoc Cancer Res; 17:120 1976

Gibbon Ape Leukemia Virus (GALV) was first isolated from a gibbon with spontaneous lymphosarcoma (Kawakami et al, Nature New Biol; 235:170) DNA from the spleen of a second animal with a spontaneous lymphosarcoma was examined for presence of sequences related to GALV RNA by molecular hybridization. At least 50% of the (^{125}I) viral RNA was found to hybridize to this DNA with a majority of the sequences being present at low frequency (approximately 1 copy per cell). In contrast, less than 10% of the (^{125}I) viral RNA hybridized to DNA from spleens of uninfected gibbons. Thermal stability measurements indicate that the proviral DNA sequences in the spleen of the leukemic gibbon were closely related, if not identical to GALV RNA. These studies suggest that the viral sequences were acquired by infection, and that integration occurred in the target tissues of the infected animal. (Author Abstract)

D. Retroviruses: Infectious DNA - Transfection of Integrated Genomes

23. VIRUS RECOVERY IN CHICKEN CELLS TESTED WITH ROUS SARCOMA CELL DNA.

Hill M, Hillova J

Gustave-Roussy Inst., Villejuif, France

Nature New Biol; 237(71):35-39 1972

The ability of a foreign DNA to enter and be integrated into the genome of chicken embryo fibroblasts was studied. After each passage, cultured chick fibroblasts were treated with DEAE-dextran and then grown for 15 min in medium containing DNA purified from nonvirus-producing Rous sarcoma virus (RSV)-transformed rat XC cells. The DNA-treated chick fibroblasts became transformed and began to produce infectious virus particles 12 to 25 days after the first XC-DNA application. Virus recovered from these cultures was able to produce sarcomas when inoculated onto chick embryo chorio-allantoic membrane, and could produce foci of transformed cells typical of those produced by RSV when applied to secondary chicken fibroblast cultures. The rescued virus was antigenically the same as the virus which originally transformed the XC cells.

24. RNA AND DNA FORMS OF THE GENETIC MATERIAL OF C-TYPE VIRUSES AND THE INTEGRATED STATE OF THE DNA FORM IN THE CELLULAR CHROMOSOME.

Hill M, Hillova J

Inst. Oncol. Immunogenetics, Villejuif, France

Biochim Biophys Acta; 355(1):7-48 1974

Literature pertaining to lines of evidence concerning the RNA and DNA forms of the virus genome of C-type viruses is reviewed. The nucleic acid composition of the C-type RNA viruses is discussed in terms of the denaturation and structure of fast-sedimenting RNA, the 4-S and 7-8-S slow-sedimenting RNA species, DNA, and attempts to define the viral genome. Evidence is then presented which suggests that a DNA intermediate is involved in the replicative cycle of C-type RNA viruses. This is defined in its relation to requirement for early DNA synthesis, continued requirement for DNA-dependent RNA synthesis, the occurrence and purification of viral reverse transcriptase and the presence of virus-specific base sequence in the DNA of normal and infected cells. The infectious proviral DNA in animals' cells infected with C-type RNA viruses is considered in terms of the uptake of foreign DNA by animal cells in vitro, the fate of foreign DNA in chicken cells, virus recovery in chicken cells treated with Rous sarcoma cell DNA, endogenous C-type RNA viruses in chicken cells, the envelope properties of viruses recovered with infectious proviral DNA, the transformation capacity of viruses recovered with infectious proviral DNA, the infectivity of double- and single-stranded forms of Rous sarcoma cell DNA, the integration of infectious proviral DNA in the cellular chromosome, and the competence of recipient cells in the occurrence of infectious proviral DNA. A model is proposed for virus replication and interaction with the cellular chromosome; this model takes into account new experimental data which is not compatible with previous concepts.

25. NUCLEAR LOCALIZATION AND COVALENT LINKAGE OF INFECTIVE VIRUS DNA OF NON-PRODUCER ROUS SARCOMA CELLS.

Hillova J, Goubin G, Coulaud D, Hill M

Inst. Cancerol. Immunogenet., Villejuif, France

J Gen Virol; 23(3):237-245 1974

DNA was extracted from nuclei or whole rat XC cells transformed with a Prague strain of Rous sarcoma virus

(RSV) to determine the location of the DNA in the cell. Chicken embryo cells (107) grown in primary culture were treated once with nuclear DNA (45.3 microg/2.5 ml of .14 M NaCl and 0.5 M-tris solution) or cellular DNA (52.5 microg/2.5 ml of .14 M NaCl and .05 M-tris solution). The specific infectivity was measured as total number of cell cultures transformed/microg DNA applied and yielded the following counts for nuclear and cellular DNA, respectively: 4/181.5 and 3/157.5. Transformed cultures produced C-type virus. XC cell DNA and SV40 reference species were centrifuged at 25,000 rpm and 4 C. The material sedimented into five regions which were assayed for infectivity. Cultures treated with regions corresponding to linear and superhelical SV40 DNA, mitochondrial DNA and fast-sedimenting fraction showed no virus production or cell transformation. One out of three cultures treated with the fraction corresponding to chromosomal 110s DNA did yield transforming virus. Inability to separate RSV DNA from chromosomal DNA via sedimentation and locating it in the nucleus of transformed cells indicates covalent bonding between the two species. Previous studies have indicated the same type of linkage between SV40 DNA and chromosomal DNA in SV40-transformed cells. The present results show separation of the SV40 reference DNA species and rule out the possibility of free viral DNA. Whether this integration is a prerequisite for virus replication remains to be demonstrated.

26. INFECTIOUS ROUS SARCOMA VIRUS AND RETICULOENDOTHELIOSIS VIRUS DNAs.

Cooper GM, Temin HM

McArdle Lab. Cancer Res., Univ. Wisconsin, Madison

J Virol; 14(5):1132-1141 1974

Quadruplicate cultures of chicken embryo fibroblasts were treated with twofold serial dilutions of DNA extracted from chicken cells infected with either Schmidt-Ruppin Rous sarcoma virus subgroup D (SR-RSV-D) or Trager duck spleen necrosis virus (TDSNV). Treatment of the recipient cells with DEAE-dextran was required for efficiency assay of infectious viral DNAs. All cultures transformed by DNA from SR-RSV-D-infected cells produced infectious RSV. The morphology of cells transformed by progeny RSV or progeny TDSNV was similar to that of the parental virus. Similar levels of infectivity were observed for DNA extracted from TDSNV-infected chicken and pheasant cells and DNA from chicken spleen cells transformed by reticuloendotheliosis virus T (REV-T). Pheasant and duck cell embryo fibroblasts were also sensitive to infection with DNA extracted from SR-RSV-D- and TDSNV-infected chicken cells. The specific infectivities of the viral DNAs corresponded to one infectious U/105 to 106 viral DNA molecules. Infection with viral DNA followed one-hit kinetics, indicating that the viral DNA is integrated into host DNA as a single unit of DNA, rather than as two or more unlinked units. The minimal size of infection RSV DNA was approximately 6 million daltons, whereas the minimal size of infectious REV DNA was 10-20 million daltons.

27. INFECTIOUS VIRAL DNA IN ROUS SARCOMA VIRUS-TRANSFORMED NONPRODUCER AND PRODUCER ANIMAL CELLS. (PP. 1015-1025)

Hill M, Hillova J, Dantchev D, Mariage R, Goubin G

Tumor Viruses Cold Spring Harbor Symposia on

Quantitative Biology. vol. 39, Cold Spring Harbor Laboratory, Cold Spring Harbor NY, 1975.

Studies of the structure and infectivity of the viral DNA of avian tumor viruses are reviewed. Nonproducer and producer Rous sarcoma virus (RSV)-transformed cells and producer nontransforming virus-infected cells were shown to harbor viral DNA specifying the respective avian tumor virus. In nonproducer Rous sarcoma cells, the residing viral DNA was linear, double-stranded, and covalently linked to the

chromosomal DNA. Both double- and single-stranded forms of RSV DNA transfected chicken cells, the progeny virus being indistinguishable from the DNA parent with respect to its morphological, biological, and antigenic properties. Unlike the DNA extracted from nonproducer RSV-transformed mammalian cells, the DNA extracted from producer RSV-transformed chicken cells gave rise, in transfection experiments, to both sarcoma virus and its nontransforming derivative. However, the DNA from nontransforming virus-infected chicken cells generated only nontransforming viruses. The frequency of nontransforming virus recovery was different from that of sarcoma virus recovery, the latter being a nonlinear function of the amount of transfecting DNA, while the former appeared to suggest a linear relationship. On the other hand, the end-point dilution of transfecting DNA for sarcoma virus recovery was approximately the same as that for nontransforming virus recovery. It is suggested that sarcoma viruses and nontransforming derivatives are recovered from two different species of viral DNA that carry or lack, respectively, the transforming genetic material. The size of double-stranded viral DNA is substantially smaller than 20×10^6 daltons. In transfection experiments, the sarcoma virus DNA was first integrated into the host cell genome before being expressed, while the nontransforming viral DNA apparently bypassed the integration step. The latter DNA appears to generate the progeny virus when taken up, carried, and transcribed in a permissive cell.

28. INFECTIOUS PROVIRAL DNA IN HUMAN CELLS INFECTED WITH TRANSFORMATION-DEFECTIVE TYPE C VIRUSES.

Nicolson MO, Hariri G, Krempin HM, McAllister RM, Gilden RV

Childrens Hosp. Los Angeles, P.O. Box 54700, Terminal Annex, Los Angeles, CA 90054

Virology; 70(2):301-312 1976

Human rhabdomyosarcoma cells (RD) were infected with the transformation-defective feline virus, RD-114, and were seen to contain viral-specific DNA integrated into the chromosomal DNA that specifies complete information for progeny virus formation. This cellular DNA is infectious for permissive cells of human and canine origin, and gives rise to progeny virus identical in assessed biochemical and biological properties to the parental virus. The host range for transfection with RD-114 DNA was similar to that of the intact virus. Although progeny virus were only first detected by reverse transcriptase assay at 2-4 wk after transfection, virus is actually released at 3 days post-transfection. The minimum dose of RD-114 DNA required for one infectious event in 2×10^6 RD cells was 0.10 to 0.20 μ g. The calculated efficiency of infection of 1 infectious unit was 5×10^4 to 5×10^5 viral gene copies, if there were 2 or 20 copies per infected cells, respectively. Approximately one in every 10^4 RD-114 treated cells was initially replicating progeny virus. RD cells, productively infected with the transformation-defective mammalian viruses FeLV and GaLV, also contained viral-specific DNA, which gave rise to the respective virus of origin upon application to permissive RD cells.

29. INFECTIVITY OF VISNA VIRUS DNA.

Haase AT, Traynor BL, Ventura PE

Veterans Admin. Hosp., 4150 Clement St., San Francisco, CA 94121

Virology; 70(1):65-79 1976

The infectivity of DNA isolated from sheep choroid plexus cells acutely infected with the RNA containing slow virus visna was investigated. This DNA was found to confer on uninfected cells the capacity to synthesize new virus. The cytopathic agent isolated in these experiments had the

biological and biochemical properties of visna virus, and the active material was established to be DNA by several criteria, the most important of which was the loss of infectivity with prior treatment of the DNA with DNase. The efficiency of infection with DNA was markedly enhanced by presenting DNA to the cell as a calcium DNA phosphate precipitate. Because of the lytic nature of visna virus infection, the infectivity of visna DNA was assayed quantitatively by plaque formation. Duplex DNA was found to be infectious, while denatured DNA was not. At least one complete copy of proviral DNA was integrated in the host genome. The minimal infective size of duplex DNA corresponded to a transcript of one subunit of viral RNA. However, the concentration dependence of infectivity was two hits over the size range of 10-30 million molecular weight. These findings suggest that the unique genetic information of the viral genome is distributed over more than one subunit and that the proviral DNA transcripts are unlinked in the cell. The usefulness of the DNA infectivity assay and the implications of the visna provirus for persistent viral infections are discussed.

30. LACK OF INFECTIVITY OF THE ENDOGENOUS AVIAN LEUKOSIS VIRUS-RELATED GENES IN THE DNA OF UNINFECTED CHICKEN CELLS.

Cooper GM, Temin HM

McArdle Laboratory for Cancer Research, University of Wisconsin, Madison, Wisconsin 53706

J Virol; 17(2):422-430 1976

The infectivity of the avian leukosis virus-related genes in the DNA of four genetically distinct types of chicken cells was determined. Infectious DNA of Rous-associated virus-0 (RAV-0) was obtained from V⁺- chicken cells which were experimentally infected with RAV-0 and from V⁺+tub⁺ chicken cells, which spontaneously produced RAV-0 and were sensitive to exogenous RAV-0 infection. However, infectious DNA of RAV-0 was not obtained from uninfected V⁺- chicken cells or from V⁺+tub⁺ chicken cells, which spontaneously produced a low titer of RAV-0 but were resistant to exogenous RAV-0 infection. No detectable amplification of the RAV-0-related DNA sequences in the V⁺+tub⁺ cells was found by hybridization of RAV-0 ³²P-labeled RNA to the DNAs of V⁺+tub⁺ and uninfected V⁺- cells. These results indicate that the endogenous avian leukosis virus-related genes in uninfected V⁺- and V⁺+tub⁺ cells differ from the RAV-0 proviruses in RAV-0-infected V⁺- and V⁺+tub⁺ cells. The lack of infectivity of the DNA of V⁺+tub⁺ cells is consistent with the hypothesis that the endogenous RAV-0 genome in V⁺+tub⁺ cells is linked to a cis-acting control element, which results in its inefficient expression.

31. INABILITY OF THE NONDEFECTIVE ROUS SARCOMA PROVIRUS TO GENERATE UPON TRANSFECTION, A TRANSFORMATION-DEFECTIVE VIRUS.

Hillova J, Hill M, Kalekine M

Dept. Cellular Molecular Biol. Inst. Cancerology Immunogenetics, Villejuif, Fran

Virology; 74(2):540-543 1976

The inability of the nondefective (nd) Rous sarcoma provirus to generate a transformation-defective (td) virus upon transfection is investigated. Six out of eight DNAs isolated from clonal lines produced only transformed cultures and no cultures containing just the td virus, whereas DNA obtained from uncloned 304 Schmidt-Ruppin-D-transformed chicken cells gave rise to both transformed and nontransformed reverse transcriptase positive cultures. Two DNA preparations from clonal cell lines (clones 47 and 48) produced nontransformed td virus-containing cultures besides transformed cultures. The fact that the cloning gave a DNA

unable to give rise to the td virus even after repeated transfections (as in the case of clones 49, 51, and 52) indicated that at least less than one-hundredth of clonal cells carried a td provirus. The td provirus could not arise from an nd provirus during the replication of the viral DNA in clonal lines of Rous sarcoma virus-transformed cells. It is suggested that the deletion in transforming functions may occur during the replication cycle of the virus either during provirus integration or during the RNA to DNA transcription. (14 refs)

32. INFECTIOUS DNA OF SPLEEN NECROSIS VIRUS IS INTEGRATED AT A SINGLE SITE IN THE DNA OF CHRONICALLY INFECTED CHICKEN FIBROBLASTS.

Battula N, Temin HM

McArdle Lab. for Cancer Res., Univ. Wisconsin, Madison, WI 53706

Proc Natl Acad Sci USA; 74(1):281-285 1977

The infectious DNA's of a number of avian leukosis-sarcoma viruses (Schmidt-Ruppin Rous sarcoma virus D, Bratislava strain 77 virus, and Prague Rous sarcoma virus C) and reticuloendotheliosis viruses spleen necrosis virus (SNV), chick syncytial virus, reticuloendotheliosis virus (strain T), and duck infectious anemia virus were digested with six nucleotide-specific restriction endonucleases, and the digests were tested for infectivity. All of the enzymes inactivated the viral infectivities except for EcoRI, which did not inactivate the infectivity of the DNA of SNV and chick syncytial virus. After digestion with EcoRI, the infectious DNA of SNV had a buoyant density in CsCl solution that was greater than the density of the high-mol-wt infectious viral DNA. The infectious EcoRI-digested SNV DNA from chronically infected chicken cells was a uniform size of 10 megadaltons, indicating that the infectious fragments were composed partly of host and partly of viral nucleotide sequences and that they were derived from a single site of integration. The infectious EcoRI-digested SNV DNA from acutely infected cells was heterogeneous in size (8-14 megadaltons), indicating multiple integration sites. These results are consistent with the hypothesis that cells that integrate infectious SNV DNA at a single site survive and multiply, whereas cells that integrate infectious viral DNA at additional sites either die or selectively lose or inactivate the DNA in the additional sites. (21 Refs)

E. Retroviruses: Genetics of Provirus Inheritance - Chromosomal Transfer of Endogenous Genomes

33. NONINFECTIOUS AKR MOUSE EMBRYO CELL LINES IN WHICH EACH CELL HAS THE CAPACITY TO BE ACTIVATED TO PRODUCE INFECTIOUS MURINE LEUKEMIA VIRUS.

Rowe WP, Hartley JW, Lander MR, Pugh WE, Teich N

Lab. Viral Diseases, Natl. Inst. Allergy and Infectious

Diseases, NIH, Bethesda, MD 20014

Virology; 46:866-876 1971

The results of studies on the number of AKR mouse cells producing virus after various periods of time in culture are described and the establishment of virus-negative cell lines that can be induced to initiate synthesis of murine leukemia virus (MLV) is reported. In AKR mouse embryo tissue cultures, the proportion of cells producing virus within 1 wk of primary culture was extremely low, ranging from 1 in 250,000 to less than 1 in 12,000,000. By 2.5 wk in culture, 12-100 x more cells had spontaneously begun to produce virus. Two cell lines which contained no detectable virus-producing cells for more than 60 serial dilutions were obtained by plating cultures with small number of AKR embryo cells. However, both cell lines and 10 clonally derived sublines have no occasion become virus-positive. This occurred either spontaneously or following experimental manipulation. The activation of virus appeared to be a very low-frequency event. Preliminary attempts to

activate AKR-type virus (N-tropic) from the cell lines by infection with a B-tropic strain proved negative. The results indicate that most, and probably all, AKR cells carry the full viral genome in an unexpressed form. (23 Refs)

34. STUDIES OF GENETIC TRANSMISSION OF MURINE LEUKEMIA VIRUS BY AKR MICE. II. CROSSES WITH FV-1**B STRAINS OF MICE.

Rowe WP, Hartley JW

Lab. Viral Diseases, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD 20014

J Exp Med; 136:1286-1301 1972

The role of the Fv-1 gene system in determining the virological characteristics of offspring of crosses between AKR mice and Fv-1**b mice was studied to determine whether the AKR chromosomal loci (V loci) which induce mouse leukemia virus (MLV) are viral genes or host genes which promote viral expression. The transmission of MLV (N-tropic type) to hybrids between AKR (which is Fv-1**n and sensitive to N-tropic virus) and Fv-1**b mice (sensitive to B-tropic virus but resistant to N-tropic) was studied. Virus was detected in a large majority of the F1 mice, but the F1 hybrid strains showed consistently delayed (6-10 wk) appearance and lower levels (10-fold) of virus than crosses with Fv-1**n mice. Backcrosses to Fv-1**b mice (b x b x AK backcrosses) yielded positive tests for virus in approx 20% of the mice, compared to 75% for n x (n x AK) backcrosses. The importance of Fv-1 in determining virus phenotype was studied in n x (b x AK) crosses; the proportion of virus-positive mice was about twice that observed in comparable backcrosses to Fv-1**b strains. Fv-1 typing of the n x (b x AK) mice demonstrated that Fv-1**n segregants were significantly (p less than 0.01 at 2 wk) more often virus-positive than Fv-1**nb segregants. Induction of virus production by iododeoxyuridine treatment of cells was not altered by the Fv-1 gene; the correlation of virus with Fv-1 in the backcrossed mice was not due to linkage between Fv-1 and one of the two V loci. The results support the idea that the V loci represent a chromosomal localization of the MLV genome, but do not constitute sufficient evidence. Alternative interpretations of the results are considered. (23 Refs)

35. GENETIC FACTORS IN THE NATURAL HISTORY OF MURINE LEUKEMIA VIRUS INFECTION: G.H.A. CLOWES MEMORIAL LECTURE.

Rowe WP

Natl. Inst. Hlth., Bethesda, Md.

Cancer Res; 33(12):3061-3068 1973

The history of tumor virology consists of four stages, the last of which has been characterized by the concept that tumor viruses are an integral part of the host. An oncogene theory to explain the expression patterns of the murine leukemia viruses (MuLV) holds that the viral genetic material is present in normal cells, that it can be expressed as infectious virus or only as viral antigens without production of virus, and that the noninfectious expression of a protein of the viral genome may be responsible for the cellular alteration leading to cancer. Studies of the MuLV in the AKR mouse revealed that the complete viral genome is an integral, heritable component of all AKR cells, that it can be present in unexpressed form, and that it does not render the cells resistant to superinfection by the same virus. Genetic and progeny studies showed that the MuLV genome is a heritable component of AKR cells and that its presence or expression in hybrids is genetically controlled. The AKR possesses two unlinked, presumably identical virus loci, and there is some indication that the virus-inducing loci are the structural genes of the virus. The virus-inducing loci are relatively stable and preliminary findings suggest that the viral genomes are not inserted at allelic sites in different

strains. Present evidence indicates that MuLV genomes are chromosomally located, with at least three genes being involved in the etiology of AKR lymphoma.

36. LEUKEMIA-SPECIFIC DNA SEQUENCES IN LEUKOCYTES OF THE LEUKEMIC MEMBER OF IDENTICAL TWINS (MEETING ABSTRACT).

Baxt W, Yates JW, Wallace HJ, Holland JF, Spiegelman S
Coll. Physicians Surg., Columbia U., New York, N. Y.
Proc Natl Acad Sci USA; 70(9):2629-2632 1973

The discovery in human leukemic cells of particulate elements encapsulating 70S RNA and RNA-directed DNA polymerase made possible the synthesis of a 3HDNA probe that could detect leukemia-specific sequences in the DNA of normal and leukemic individuals. An earlier study of a series of unrelated leukemic patients established that the nuclear DNA of their leukemic cells contain particle-related sequences that cannot be detected in leukocytes of normal individuals. This result was inconsistent with the virogene concept that demands the inclusion of one complete copy of oncogenic information in the genome of every normal cell. The same difference between leukemic patients and normal individuals was found in the present study of two sets of identical twins, each set containing a member with acute myelotic leukemia. In each pair, the leukemic member contained particle-related sequence in the DNA of his leukocytes that could not be detected in the leukocytes of his healthy identical sibling. This finding implies that the additional leukemia-specific information found in the DNA of the leukemic individuals must have been inserted subsequent to fertilization. This outcome argues against the virogene hypothesis or any other etiologic concept that invokes vertical transmission through the germ line of the particle-related information found uniquely in the DNA of leukemic cells.

37. DEFINITIVE EVIDENCE THAT THE MURINE C-TYPE VIRUS INDUCING LOCUS AKV-1 IS VIRAL GENETIC MATERIAL (MEETING ABSTRACT).

Chattopadhyay SK, Rowe WP, Teich NM, Lowy DR
Natl. Inst. Allergy Infect. Dis., Bethesda, Md.
Proc Natl Acad Sci USA; 72(3):906-910 1975

Inheritance of the Akv-1 locus (one of the two murine leukemia virus (MuLV)-inducing loci of the AKR mouse strain) and AKR-specific viral DNA sequences (DNA sequences homologous to a portion of MuLV RNA) was studied in AKR/J (Akv-1+, Gpi-1b, c), NIH Swiss (Akv-1-, Gpi-1b, c), and C57Br/J (Akv-1-, Gpi-1a, c+) mice, and hybrid crosses between these strains. Cellular DNA from 15- to 18-day embryos was hybridized with a viral (3H)DNA probe and the segregation of viral sequences with virus inducibility was studied. When cellular DNA was hybridized with a Gross-AKR type MuLV probe, the virus-yielding and non-virus-yielding mouse strains differed with regard to: the proportion of probe sequences hybridized to the cell DNA; the number of classes of probe sequences represented in the cell DNA; and the thermal denaturation characteristics of the cell-probe hybrid molecules. Three-point genetic crosses involving Akv-1, Gpi-1, and c on individual mouse embryos indicated that a portion of the cell DNA hybridizable with the viral probe sequences segregated with Akv-1; this finding strongly suggested that the Akv-1 locus contains viral sequences. Quantitation of the viral sequences in Akv-1 congenic mice showed that the AKR DNA contains three to four copies of the AKR-specific viral sequences, while the NIH DNA contains only one class of viral sequences; in the case of the AKR DNA, the AKR-specific viral sequences were well matched to the viral (3H)DNA, while those of the NID DNA were poorly matched to the probe. The data suggest that the Akv-1 virus-inducing locus may contain more than one copy

of these sequences and that a larger number of copies may be the result, rather than the cause, of a high level of virus inducibility.

38. INFECTION OF DEVELOPING MOUSE EMBRYOS WITH MURINE LEUKEMIA VIRUS: TISSUE SPECIFICITY AND GENETIC TRANSMISSION OF THE VIRUS.

Jaenisch R, Dausman J, Cox V, Fan H, Croker B
Salk Inst., San Diego, CA 92112
Haematol Bluttransfus; 19:341-356 1976

The tissue specificity of Moloney leukemia virus (M-MuLV) was studied by infecting BALB/c mice at two different stages of development. Either newborn mice, which can be considered as fully differentiated animals, were infected with M-MuLV or preimplantation mouse embryos were infected in vitro at the 4-8 cell stage, a stage of development before differentiation has occurred. After surgical transfer of the embryos to the uteri of pseudopregnant surrogate mothers, the latter developed to term and adult mice. In both cases, animals were obtained that had developed an M-MuLV induced leukemia. Molecular hybridization tests for the presence of M-MuLV-specific sequences revealed that mice infected as newborns carried M-MuLV-specific sequences in target tissues only, ie, thymus, spleen, lymph nodes, or organs infiltrated by tumor cells. In contrast, when leukemic animals derived from M-MuLV-infected preimplantation embryos were analyzed, virus-specific sequences were detected in both target tissues and nontarget tissues such as the liver, kidney, brain, testes, and germ line. RNA was extracted from different tissues of an animal infected at the preimplantation stage to study the expression of the viral DNA integrated in target and nontarget organs, and 50-100 X more M-MuLV-specific RNA was detected in tumor tissues than was found in nontarget organs. Since all organs contained the same amount of virus-specific DNA, the integrated virus genome can apparently be differentially expressed in different tissues. Mice infected at the preimplantation stage had M-MuLV integrated into their germ line. Virus transmission from the father to the offspring occurred according to simple Mendelian expectations. Molecular hybridization tests revealed that the virus was integrated into the germ line at only one out of two or three possible integration sites. During the development of leukemia, amplification of this virus copy was observed in the target tissues only and not in nontarget tissues. (25 Refs)

39. VIABLE HYBRIDS BETWEEN LETHALLY X-IRRADIATED HAMSTER CELLS AND UNIRRADIATED MOUSE CELLS.

Jullien P, Lawrence D
Unite de Physiologie Cellulaire de l'I.N.S.E.R.M., Institut du Radium Faculte des Sciences, Batiment 110-91405
Orsay Cedex, France
Int J Radiat Biol; 30(3):277-282 1976

Sendai virus-induced fusion between heavily x-irradiated (4,000 R) hamster cells, BHK21 or RS2-3 (BHK21 cells transformed by Rous sarcoma virus) and unirradiated mouse cells, A9 or c11D, gave rise to hybrids. The colonies were visible after 15 days of culture; their growth was slow for a further 2 wk, giving the impression that only some cells continued to divide and that others were incapable of doing so. The hybrids possessed both mouse and hamster surface antigens. RS2-3 x mouse hybrids did not form heterokaryons with chick-embryo fibroblasts producing infectious Rous sarcoma virus, although in control assays with RS2-3 substituted for hybrid cells there was a massive transformation of chicken fibroblasts after 10 days in culture. Two explanations are offered for the absence of RSV induction with hybrid cells: (1) the RSV provirus is integrated in

irradiated hamster chromosomes eliminated from the hybrids; or (2) the viral genome is still present but the presence of mouse chromosomes prevents the formation of infectious virus after fusion with chicken fibroblasts. (19 refs)

40. GERM LINE INTEGRATION OF MOLONEY LEUKEMIA VIRUS: EFFECT OF HOMOZYGOSITY AT THE M-MuLV LOCUS.

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Universität Hamburg, Martinstrasse 52, 2000 Hamburg
20, W. Germany
Cell (Camb); 12(3):691-696 1977

The role of homozygosity in the normal development of mice genetically transmitting Moloney leukemia virus (M-MuLV) was investigated. Hybridization of M-MuLV complementary DNA (cDNA) to liver DNA of heterozygous animals revealed an av of 1.2 copies of M-MuLV per diploid mouse genome equivalent; the corresponding figure for the DNA of leukemic spleens was 5.7 copies per genome. Embryos of heterozygous animals female (+-) x male (+-) revealed three classes of M-MuLV DNA annealing with cDNA; the first class carried two copies of M-MuLV-specific sequences per genome, the second one copy, and the third no M-MuLV specific sequences. In further mating experiments, the offspring were allowed to survive, and hepatectomy was performed at 6 to 8 wk. The same three classes of offspring were noted in a ratio of approx 1:2:1; all animals were viremic, having been infected congenitally by the mother. Mating of the F1 generation revealed that transmission followed classical Mendelian formulas. These results indicate that homozygosity at the M-MuLV locus has no detectable effect on normal development. A mouse colony of animals homozygous at the M-MuLV locus was established. (25 Refs)

41. GERM LINE INTEGRATION AND LEUKEMOGENESIS OF EXOGENOUS AND ENDOGENOUS MURINE LEUKEMIA VIRUSES. (PP. 283-310)

Jaenisch R, Berns A, Dausman J, Cox V

Animal Virology, ICN-UCLA Symposia on Molecular and Cellular Biology. Baltimore D, Huang AS, Fox CF, ed. New York, Academic Press Inc, Vol. 4, 1976.

The conversion of exogenous virus into endogenous virus with Moloney murine leukemia virus (M-MuLV) by infecting BALB/129 newborn mice or preimplantation mouse embryos at the 4-to 8-cell stage is described. Both newborns and embryos developed an M-MuLV-induced leukemia. Mendelian transmission of M-MuLV occurred in the progeny of the sons, grandsons, and great grandsons of the infected animal. It was possible to calculate from the data that one-half copy of M-MuLV per haploid, or one copy per diploid, mouse genome equivalent is present in the "nontarget" organs of viremic N-1 and N-2-generation animals. During leukemogenesis the number increases to a max of two copies per haploid mouse genome. The data strongly suggest that subsequent generation animals are heterozygous for one locus responsible for M-MuLV synthesis. In additional experiments, a study was made of leukemogenesis in AKR mice that carry the endogenous Gross-MuLV in their germ line, to see whether the leukemia is accompanied by an increase in the number of AKR virus-specific genes in the tumor tissues. AKR virus-specific sequences were amplified in the "target" cells of leukemic AKR mice, but not in the "nontarget" cells. (31 Refs)

F. Retroviruses: Cellular Control of Integration and the Fv-1 Locus

42. EFFECT OF FV-1 GENE PRODUCT ON PROVIRAL DNA FORMATION AND INTEGRATION IN CELLS INFECTED WITH MURINE LEUKEMIA VIRUSES.

Jolicoeur P, Baltimore D

Institut de Recherches Cliniques de Montreal, 110 Ouest
Avenue des Pins, Montreal, Canada
Proc Natl Acad Sci USA; 73(7):2236-2240 1976

The synthesis of proviral DNA and its integration into cellular DNA were studied in Fv-1n/n mouse cells (strains NIH/3T3, SIM) resistant to B-tropic murine leukemia viruses and in Fv-1b/b cells (strains JLS-V9, SIM.R) resistant to N-tropic viruses. The amounts of unintegrated murine leukemia virus-specific DNA detected by molecular hybridization in extracts of Fv-1n/n or Fv-1b/b cells after infection with N- or B-tropic viruses were the same in both permissive and resistant cells. Therefore, formation of DNA products from the viral RNA template does not appear to be grossly affected by the Fv-1 gene product. Integration of virus-specific DNA into chromosomal cellular DNA was assayed by hybridization of radioactive complementary DNA to DNA from infected cells. With either NIH/3T3 or SIM.R cells infected with N- or B-tropic viruses, integration of proviral DNA could be detected in permissive cells but not in nonpermissive cells. The Fv-1 gene product therefore appears to prevent integration of proviral DNA.

43. HOST RESTRICTION OF FRIEND LEUKEMIA VIRUS: PROTEINS AND MESSENGER RNA. (PP. 257-268)

Socero R, Sveda MM, Krontiris TG, Ray U

Animal Virology, ICN-UCLA Symposia on Molecular and Cellular Biology. Baltimore D, Huang AS, Fox CF, ed. New York, Academic Press Inc, Vol. 4, 1976.

The mechanism of Fv-1-induced host restriction, particularly late events in the viral replication cycle, was investigated. Murine oncornavirus host restriction is multigenic, and only the host gene Fv-1 controls the ability of particular oncornaviruses to replicate in tissue culture or produce leukemia. Total and viral envelope synthesis was studied to determine whether the Fv-1 gene effect was at the level of control of translation or assembly of viral proteins. In addition, the amounts of viral-specific messenger RNA (mRNA) in the cytoplasm and nucleus of the infected cell were determined. The results do not indicate directly the site of the Fv-1 gene effect on the replication of Friend leukemia virus. They suggest that the site of action is early, perhaps at synthesis or integration of the provirus, or at its transcription. Since there are no cell-associated viral proteins present, it is concluded that the host-restriction phenomenon does not act at the level of viral assembly. Analysis of the proteins shows no evidence of a faulty processing of viral precursor proteins. Decreases in viral-specific functioning mRNA suggest that the host-restricting effect is not due to inhibition of the translation of viral mRNA. (16 Refs)

44. FV-1 MEDIATED HOST RESTRICTION OF FRIEND LEUKEMIA VIRUS.

Sveda MM

Yeshiva Univ., New York, NY 10033
Diss Abstr Int B; 37(5): 2031B-2032B 1976

The host restriction of murine cells to exogenous infection by murine leukemia viruses was investigated by comparing the replication steps of Friend Leukemia virus (LLV-F) in permissive infections and nonpermissive infections. When nuclear-associated radioactive nucleic acids were analyzed, two distinct species of RNA-DNA covalent hybrids were

found. Equal amounts of these hybrids were found in permissive and nonpermissive infections; this indicates that equivalent activation of reverse transcriptase has occurred. RNA-DNA hybrids at rho 1.44 g/cc were shown to be viral RNA covalently linked to host cell DNA. Equivalent amounts of these hybrids were found in permissive and nonpermissive infections. It was concluded that Fv-1 mediated host restriction was not affecting provirus integration. A transcriptional control mechanism was postulated for Fv-1. Further studies indicated that integration of proviral DNA with host cell DNA was present under permissive conditions and not under nonpermissive ones. Fv-1 mediated host restriction of LLV-F thus appears to affect the events leading to the integration of proviral DNA. (0 Refs)

45. EFFECT OF FV-1 GENE PRODUCT ON SYNTHESIS OF N-TROPIC AND B-TROPIC MURINE LEUKEMIA VIRAL RNA.

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Dept. Biology, Massachusetts Inst. Technology, 77
Massachusetts Ave., Cambridge, MA 02139
Cell (Camb); 7(1):33-39 1976

The production of virus and the synthesis of virus-specific RNA were studied in Fv-1n/n (NIH/3T3, SIM) and Fv-1b/b (BALB/3T3, SIM.R) cell lines after infection with N- or B-tropic MuLV. Virus production, measured by reverse transcriptase activity in the medium, was 70-100 fold lower in cells resistant at the Fv-1 locus than in permissive cells. The virus-specific RNA, detected by hybridization in RNA excess with complementary DNA, was reduced by approximately 70-100 fold in cytoplasm of resistant cells compared to permissive cells. There was also reduction of the same magnitude in the levels of virus-specific RNA extracted from nuclei of resistant cells. The data therefore show that virus-specific RNA levels are reduced in cells nonpermissive at the Fv-1 locus, suggesting that restriction of the Fv-1 gene product occurs at the level of transcription of the viral genome or at a pre-integration step, or, alternatively, that the RNA transcripts are rapidly degraded after their synthesis.

46. HOST RESTRICTION OF FRIEND LEUKEMIA VIRUS: SYNTHESIS AND INTEGRATION OF THE PROVIRUS.

Sveda MM, Soeiro R

Dept. Medicine, Albert Einstein Coll. Medicine, Bronx, NY 10461

Proc Natl Acad Sci USA; 73(7):2356-2360 1976

The mechanism of host restriction of exogenous infection by murine leukemia viruses was investigated by comparing the early events in the replication of N-tropic versus B-tropic Friend leukemia virus in NIH 3T3 cells, which are Fv-1nn in type, permissive for the N-tropic strain and nonpermissive for the B-tropic strain. The synthesis, intracellular location, and molecular form of virus-specific DNA early in replication were studied by molecular hybridization with a virus-specific DNA probe. The results suggested that in the permissive infection viral DNA rapidly becomes integrated with cellular DNA. However, in the nonpermissive infection, although almost equal amounts of both positive and negative strand viral DNA are synthesized, the provirus is not integrated. (32 refs)

47. MECHANISM OF FV-1 LOCUS INHIBITION OF MURINE LEUKEMIA VIRUSES: STUDIES BY DNA TRANSFECTION (MEETING ABSTRACT).

Yang WK, Hsu IC, Boone LR, Tennant RW, Brown A
Oak Ridge Natl Lab, Oak Ridge, TN 37830
Proc Am Assoc Cancer Res; 18:149 1977

Virion infection of N- and B-tropic murine leukemia viruses (MuLV) is inhibited respectively in mouse cells of Fv-1**b and Fv-1**n genotypes. Here we study this aspect of

host-virus interaction by DNA transfection, with which the reverse transcription step is not required for establishing the oncornavirus infection. NIH Swiss mouse 3T3 (Fv-1**n) cells were treated with "sheared" DNAs isolated from SC-1 cells infected with N- or B-tropic MuLV, subsequently cocultivated with SC-1 cells and serially subcultured. Detection of progeny MuLVs by the XC plaque assay demonstrated that ID50's in NIH 3T3 cells were 1.3 mug for N-MuLV DNA preparation and 1.9 mug for the B-MuLV DNA preparation. Similar quantitative results were obtained in BALB/c SV-A31 and C57BL/6 mouse embryo cultured (Fv-1**b) cells with these DNA preparations. This indicates that the mouse Fv-1 gene product does not inhibit the integration and subsequent expression of cell genome-associated MuLV proviral DNA. The DNA transfection method can also be employed to assess the integration activity of newly synthesized un-integrated proviral DNAs derived from early stage of virion infection. (Author Abstract)

48. CELLULAR FUNCTIONS ARE REQUIRED FOR THE SYNTHESIS AND INTEGRATION OF AVIAN SARCOMA VIRUS-SPECIFIC DNA.

Varmus HE, Padgett T, Heasley S, Simon G, Bishop JM
Dept. Microbiology, Univ. California, San Francisco, CA 94143

Cell (Camb); 11(2):307-319 1977

We have used two experimental strategies to test the role of cellular functions in the synthesis and integration of virus-specific DNA in cells infected by avian sarcoma virus (ASV). First, quail embryo fibroblasts placed in stationary phase (G0) by prolonged serum starvation did not support the efficient synthesis of viral DNA during the first 24-48 hr after infection. Synthesis of viral DNA was impaired according to at least two parameters: the amount of DNA was diminished, particularly the amount of the plus-strand DNA (identical in polarity to the viral genome); and the length of both minus and plus strands was reduced in the stationary cells. In parallel cultures fed with fresh serum, over two-thirds of the cells were able to reenter the cell cycle within 24 hr, and viral DNA of normal size was synthesized. Second, density labeling of viral and cellular DNA with 5-bromodeoxyuridine was used to determine whether cellular DNA synthesis was required for integration of viral DNA. In both quail embryo fibroblasts released from G0 by serum replacement and randomly growing duck embryo fibroblasts, viral DNA was integrated only into cellular DNA replicated during the infection. Our results indicate that serum-starved cells lack a factor (or factors) required for the efficient and complete synthesis of ASV-specific DNA. We have not been able to establish whether such factor(s) are present in growing cells only during S phase. Integration of viral DNA appears to require cellular DNA synthesis; this may be due to a requirement for a factor (or factors) present in adequate concentration only during S phase or to a requirement for the structural changes in cellular DNA that accompany replication. (Author abstract) (58 Refs)

G. Retroviruses: Restriction Endonuclease and the Southern Gel-Filter Blotting Technique

49. INTEGRATION OF AVIAN SARCOMA VIRUS DNA SEQUENCES IN TRANSFORMED MAMMALIAN CELLS.

Collins CJ, Parsons JT

Dept. Microbiology, Univ. Virginia Medical Sch.,
Charlottesville, VA 22901

Proc Natl Acad Sci USA; 74(10):4301-4305 1977

DNA from six avian sarcoma virus (ASV)-transformed mammalian cell lines was digested with the restriction endonucleases EcoRI, Xho I, or Sal I, fractionated by agarose gel electrophoresis, transferred to nitrocellulose filter strips,

and hybridized with specific ASV ³²P-complementary DNA (cDNA) probes. DNA from all the ASV-transformed cell lines yielded three common virus-specific DNA fragments (2.4, 1.8, and 1.3 x 10⁶ daltons) upon cleavage with EcoRI. Xho I appeared to cleave at least once within the integrated provirus, and it yielded a common fragment of 3.3 x 10⁶ daltons as well as a second virus-specific DNA fragment whose size varied from 4.0 to 5.0 x 10⁶ daltons in the different transformed cell lines. Sal I did not cleave within the provirus, and it yielded a single major virus-specific fragment of about 11 x 10⁶ daltons in all transformed lines examined. The cDNA probes showed that the 1.8 x 10⁶-daltons EcoRI fragment contains sequences homologous to the 3' end of the viral RNA as well as to the src region of the viral genome. These studies demonstrate that the same region on the ASV genome is utilized for provirus integration in different ASV-transformed cell lines. (2i Refs)

H. Retroviruses: Studies of the Chromatin Carrying Integrated Genomes

50. IN VITRO TRANSCRIPTION OF RNA TUMOR VIRUS GENES IN THE CHROMATIN OF UNINFECTED CHICKEN CELLS.

Astrin SM

Fox Chase Cancer Ctr., Philadelphia, Pa.

Biochem Biophys Res Commun; 61(4):1242-1248 1974

Chromatin isolated from chicken embryo cells, which have been shown to contain sequences of tumor virus DNA in an integrated state, was transcribed in vitro with E coli RNA polymerase and the transcripts were assayed for the presence of viral RNA. RNA transcribed from the chromatin of cells in which viral gene functions are expressed contained readily detectable quantities of viral RNA; in contrast, RNA transcribed from chromatin of cells (in which viral gene functions are expressed poorly or not at all) contained little, if any, viral RNA. These results parallel the results obtained with RNA isolated from the two cell types. The findings indicate that the control mechanism regulating the transcription of endogenous viral genes in chicken cells can be studied in an in vitro system with isolated chromatin.

51. SELECTIVE DEGRADATION OF INTEGRATED MURINE LEUKEMIA PROVIRAL DNA BY DEOXYRIBONUCLEASES.

Panet A, Cedar H

Dept. Virology, Hebrew Univ.-Hadassah Medical Sch., Jerusalem, Israel

Cell; 11(4):933-940 1977

The sensitivity to micrococcal nuclease and DNAase I of the integrated proviral DNA sequences in Swiss mouse cells infected with Moloney murine leukemia virus has been studied. Chromatin was separated into micrococcal nuclease-sensitive and -resistant regions, and the amount of proviral sequences in these DNA preparations was estimated by kinetic hybridization with single-stranded complementary DNA of Moloney murine leukemia virus. At least two thirds of the proviral DNA sequences were found in the open regions of chromatin, and only one third was resistant to nuclease. The proviral DNA sequences are even more sensitive to deoxyribonuclease I. When intact nuclei were treated with limited amounts of enzyme, only 5% of the nuclear DNA was digested, whereas 48% of the proviral DNA was degraded. The proviral DNA sequences in cells which do not produce virus are more resistant to nuclease digestion, as compared to virus producer cells. Thus the endogenous proviral sequences, in normal uninduced Swiss mouse cells, are randomly distributed between resistant and sensitive portions of chromatin when tested with either micrococcal nuclease or pancreatic deoxyribonuclease I. The effect of cell cycle synchronization on the accessibility of the proviral sequences to pancreatic

deoxyribonuclease I was investigated with rat cells infected with Moloney murine leukemia virus. The amount of proviral DNA sensitive to pancreatic deoxyribonuclease I is higher in actively dividing cells than in cells arrested at G0 phase, which produce only small amounts of virus. (Author abstract) (23 Refs)

II. APPROACHES FOR THE STUDY OF INTEGRATED PAPOVAVIRUS GENOMES

A. Papovaviruses: Nucleic Acid Hybridization Kinetics

52. QUANTITATION OF SIMIAN VIRUS 40 SEQUENCES IN AFRICAN GREEN MONKEY, MOUSE AND VIRUS-TRANSFORMED CELL GENOMES.

Gelb LD, Kohne DE, Martin MA

Lab. Biology of Viruses, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD 20014

J Mol Biol; 57:129-145 1971

DNA re-association kinetics on hydroxyapatite were used to determine the number of simian virus (SV)40 genome equivalents present in green monkey and SV40-transformed mammalian DNA's. A control reaction using salmon DNA representing 0.50 copy of SV40 DNA per mammalian cell gave a C0t (the product of the nucleic acid concentration (C0) and the time (t) of the re-association incubation expressed as moles of nucleotides x sec/liter) of 2.9 x 10⁻⁴ for half re-association (C0t1/2). An experimental reaction with green monkey DNA gave a C0t1/2 of 1.25 x 10⁻⁴, 2.32 x faster than that of the salmon control. This indicated that normal green monkey DNA contains the equivalent of 0.66 copy of SV40 DNA per cell. The av value of SV40 DNA equivalents per green monkey cell, determined with seven preparations was 0.50. The virus-transformed cell lines SV-UV-15 clone 1, SVPy3T3-11, SVT2, SV40 hamster tumor, and SV-UV-15 clone 5 contained 1.04, 1.42, 1.56, 2.08, and 3.86 SV40 genome equivalents per mammalian diploid cell, respectively. The results indicate that it is possible to detect less than one SV40 DNA equivalent per mammalian cell genome using the kinetics of DNA reassociation. The biological significance of the results are discussed. (27 Refs)

53. LOSS OF SIMIAN VIRUS 40 DNA-RNA HYBRIDS FROM NITROCELLULOSE MEMBRANES: IMPLICATIONS FOR THE STUDY OF VIRUS-HOST DNA INTERACTIONS (MEETING ABSTRACT).

Haas M, Vogt M, Dulbecco R

Salk Inst., San Diego, Calif.

Proc Natl Acad Sci USA; 69(8):2160-2164 1972

SV40 viral DNA, isolated from monkey cells infected with SV40 at high and low multiplicities of infection was hybridized with SV40 complementary RNA (cRNA). Hybridization mixtures were incubated for 16-18 hr and maintained on nitrocellulose membranes. Extensively hybridized DNA was not retained by the membranes; the amount of viral DNA retained by membranes dropped rapidly, especially with DNA from cells infected at high SV40 multiplicities. The loss of DNA-RNA hybrid molecules was not prevented by addition of hamster or E coli DNA to incubation mixtures. SV40-transformed hamster cell DNA-RNA hybrids were retained on membranes if DNA fragments were relatively long. They were not retained if DNA fragments were sheared to 100,000 daltons/single strand (less than the length of the SV40 DNA molecule). Apparently, each of the six genomes/cell in SV40-transformed cells was individually integrated.

54. TRANSCRIPTION OF SIMIAN VIRUS 40. II. HYBRIDIZATION OF RNA EXTRACTED FROM DIFFERENT LINES OF TRANSFORMED CELLS TO THE SEPARATE STRANDS OF SIMIAN VIRUS 40 DNA.

Ozanne B, Sharp PA, Sambrook J
Cold Spring Harbor Lab., N.Y.
J Virol; 12(1):90-98 1973

The amount of simian virus 40 (SV40) DNA present in various SV40-transformed mouse cell lines and "revertants" isolated from them was determined. The number of viral DNA copies in the different cell lines ranged from 1.35-8.75 copies/diploid quantity of host DNA and from 2.2-14 copies/cell. The revertants had the same number of viral DNA copies/diploid quantity of mouse cell DNA as their parental cell lines; however, they showed an increased number of viral DNA copies/cell due to their increased amount of DNA. By using separated strands of SV40 DNA, the extent of each DNA strand transcribed into stable RNA species was determined for the transformed and "revertant" cell lines. From 30-80% of the "early" strand and from 0-20% of the "late" strand was present as stable RNA species in the cell lines tested. There was no alteration in the pattern of the stable viral RNA species present in three concanavalin A-selected revertants, whereas in a fluorodeoxyuridine-selected revertant there was less viral-specific RNA present in the cells.

55. SIMIAN VIRUS 40 DNA INTEGRATION WITHIN THE GENOME OF VIRUS-TRANSFORMED MAMMALIAN CELLS.

Gelb LD, Martin MA
Natl. Inst. Hlth., Bethesda, Md.
Virology; 51(2):351-357 1973

The location of integrated SV40 DNA in a series of virus-free transformed murine cells was analyzed by characterizing the reiteration frequency of adjacent host cell DNA sequences. Cellular DNA was mechanically sheared to fragments approximately 8×10^6 or 7×10^5 daltons in size, separated into reiterated and nonreiterated fractions, and then examined for the presence of SV40 DNA. SV40 DNA sequences were associated with the nonreiterated fraction of mammalian DNA in each of the cell lines examined. In addition, the pattern of viral DNA distribution between the repetitive and unique cellular DNA fractions varied from cell line to cell line suggesting that integration of SV40 DNA may occur at different sites in each cell line examined.

56. VIRAL DNA SEQUENCES IN CELLS TRANSFORMED BY SIMIAN VIRUS 40, ADENOVIRUS TYPE 2 AND ADENOVIRUS TYPE 5.

Sambrook J, Botchan M, Gallimore P, Ozanne B, Pettersson U, Williams J, Sharp PA
Cold Spring Harbor Lab., Cold Spring Harbor, NY 11724
Cold Spring Harbor Symp Quant Biol; 39:615-632 1974

Cleavage with the restriction endonucleases EcoRI and HpaI followed by hybridization studies were used to measure the quantity of specific fragments of viral DNA in rat cells transformed by adenovirus 2, in hamster cells transformed by adenovirus 5, and in mouse cells transformed by simian virus (SV)40. P32-labeled adenovirus 2 DNA was digested with EcoRI and HpaI and the specific fragments obtained were used to assay for the presence of adenovirus 2 DNA sequences in 10 different lines of transformed rat cells. The renaturation of each specific fragment was measured in the presence of DNA extracted from the transformed cells, calf thymus DNA, and calf thymus DNA to which unlabeled viral DNA had been added. F17 cells contained 3.5 copies, F18 cells, 2.9 copies, F19 cells, 4.9 copies, B1 cells, 6.0 copies and 2T4 cells, 6.9 copies of the viral sequences per diploid quantity of cellular DNA. The four remaining cell lines showed patterns of hybridization

which were very different from those displayed by the other six cell lines. The results showed that none of the rat cell lines transformed by adenovirus 2 contained a complete set of viral genes. However, all 10 lines contained the segment of viral DNA that extended from the left-hand end to a point about 14% along the genome. This sequence must code for any viral functions necessary for the maintenance of the transformed state. Two lines of hamster cells transformed by adenovirus 5, HT14a and HT14b, contained 2.4 copies and 5.5 copies of the cleavage fragments per diploid quantity of cellular DNA, respectively. Neither of these transformants contained a complete set of the viral sequences. In mouse cells transformed by SV40 the total wt of the viral DNA was calculated to be approx 4.17 genome equivalents per diploid quantity of cellular DNA. The lengths of the fragments obtained by digestion and their map positions along the viral genomes were also determined. (37 Refs)

B. Papovaviruses: Centrifugation in Gradients to Demonstrate Integration

57. INTEGRATION OF SIMIAN VIRUS 40 DEOXYRIBONUCLEIC ACID INTO THE DEOXYRIBONUCLEIC ACID OF PRIMARY INFECTED CHINESE HAMSTER CELLS.

Hirai K, Lehmian J, Defendi V
Wistar Inst. Anatomy and Biology, Philadelphia, PA 19104
J Virol; 8(5):708-715 1971

The integration of simian virus (SV)40 DNA into the DNA of primary infected Chinese hamster cells (ChH) was investigated. Nuclei from monolayers of ChH cells infected with SV40 were isolated at various times after infection and the DNA was extracted. The association of SV40 DNA with cellular DNA was first detectable at 10-15 hr postinfection, when cellular DNA synthesis occurred. The proportion of DNA hybridizable with SV40 3H-complementary RNA (3H-cRNA) increased rapidly and reached a plateau at about 30 hr after infection. By 30 hr, no free SV40 DNA could be detected by hybridization with SV40 3H-cRNA. However, a large amount of DNA extracted from the ChH cells was able to hybridize with SV40 3H-cRNA. The integration process was not affected by D-arabinosyl cytosine but was partially inhibited by cycloheximide. Reconstruction experiments with various combinations of SV40 DNA and numbers of nuclei showed that a max of only 3% of the input viral DNA was found as a contaminant in the high mol wt cell DNA fractions. Up to 90% of DNA hybridizable with SV40 cRNA was observed in the high mol wt cellular DNA fractions of gradients of nuclei from infected cells at 30 hr postinfection. The results indicated that the SV40 DNA was covalently linked to the cellular DNA. The results also indicated a good chronologic and quantitative correlation between integration and induction of cellular DNA synthesis and tumor (T) antigen. (19 Refs)

58. INTEGRATION OF SIMIAN VIRUS 40 DEOXYRIBONUCLEIC ACID INTO THE DEOXYRIBONUCLEIC ACID OF PERMISSIVE MONKEY KIDNEY CELLS.

Hirai K, Defendi V
Wistar Inst. Anatomy Biol., Philadelphia, Pa.
J Virol; 9(4):705-707 1972

The integration of SV40 DNA into the genome of permissive African green monkey kidney (CV-1) cells was studied by DNA-RNA hybridization. Infected confluent CV-1 cultures were split and grown in D-arabinosyl cytosine (Ara-C, 15 microg/ml). At various times thereafter, DNA was purified from isolated nuclei by the pH phenol method and CsCl equilibrium density centrifugation. Association of SV40 DNA to CV-1 DNA began at about 20 hr postinfection and

remained at a constant level up to about 48 hr. The total amount of free SV40 in nuclei progressively decreased. Alkaline sucrose gradient centrifugation of a mixture of 14C- leucine- and 14C- lysine -labeled CV-1 nuclei and 3H-labeled SV40 DNA showed that nuclear DNA was clearly separated from SV40 DNA and protein. At 6 hr postinfection, most of the DNA hybridizable with 3H-labeled SV40 complementary RNA (c-RNA) was present in the fractions representing free SV40 DNA. However, at 30 hr post-infection most of the hybridizable DNA was associated with high-molecular-weight cellular DNA by alkali-stable linkages. When CV-1 cells were infected in the absence of Ara-C, a large fraction of the DNA hybridizable with SV40 cRNA was found in the fraction corresponding to SV40 DNA component I (53S). The specific activity of hybridizable DNA in the faster-sedimenting fractions was similar to that in the corresponding fractions of cells infected in the presence of Ara-C. It was thus concluded that SV40 DNA was integrated into the DNA of CV-1 cells during the early phases of the replicative cycle of the virus.

59. FATE OF INFECTING SIMIAN VIRUS 40-DEOXYRIBONUCLEIC ACID IN NONPERMISSIVE CELLS: INTEGRATION INTO HOST DEOXYRIBONUCLEIC ACID.

Collins CJ, Sauer G

German Cancer Res. Ctr., Heidelberg, West Germany
J Virol; 10(3):425-432 1972

A kinetic analysis of conformational changes of simian virus 40 (SV40) donor DNA on infection of nonpermissive 3T3 cells is reported. Nonpermissive 3T3 cells were infected with purified superhelical SV40 deoxyribonucleic acid I (DNA I). One hour after infection, approximately 60% of the intracellular SV40 DNA was converted to relaxed forms. One day after infection, all intracellular SV40 DNA was present as slow-sedimenting material, and no SV40 DNA I was detectable. At 2 days after infection there appeared viral DNA sequences cosedimenting with cellular DNA during alkaline velocity centrifugation. Furthermore, by both alkaline equilibrium gradient centrifugation and by DNA-ribonucleic acid hybridization analysis, covalent linkage of viral DNA sequences to cellular DNA was demonstrated. Integration of SV40 DNA into cellular DNA did not appear to require DNA synthesis, although DNA synthesis followed by mitotic division of the cells enhanced the amount of viral DNA integrated. Based on data obtained by two different methods, it was calculated that 1,100 to 1,200 SV40 DNA equivalents must be integrated per cell by 48 hr after infection.

60. INTEGRATION OF SV40 DNA AND INDUCTION OF CELLULAR DNA SYNTHESIS AFTER A TS SV40 INFECTION.

Hirai K, Robb JA, Defendi V

Wistar Inst. Anat. Biol., Philadelphia, Pa.

Virology; 59(1):266-274 1974

The early temperature-sensitive mutant of simian virus 40 (SV40), ts*101, was characterized in nonpermissive Chinese hamster (ChH) and permissive monkey CV-1 cells for integration of viral DNA and induction of cellular DNA synthesis. At 42 C, this mutant did not induce the synthesis of T antigen, cellular DNA, or viral DNA in CV-1 cells. The viral DNA did not integrate into the CV-1 DNA, although nuclear penetration did occur. In the ChH cells, ts*101 induced the synthesis of T antigen at 40 C and 42 C, and the viral DNA integrated into the ChH DNA; however, ChH DNA synthesis was not induced. These findings suggest that the integration precedes the induction of cellular DNA synthesis. The results also indicate that some function(s) related to the early phase of SV40 infection is regulated and/or provided by the host cell.

61. INTEGRATION OF PROGENY SIMIAN VIRUS 40 DNA INTO THE HOST CELL GENOME.

Holzel F, Sokol F

Wistar Inst. Anat. Biol., Philadelphia, Pa.

J Mol Biol; 84(1):423-444 1974

A study was made, by means of nucleic acid hybridization techniques, of progeny simian viral 40 DNA integration into the host cell DNA. Purification included precipitation of cellular DNA, velocity centrifugation (in alkaline sucrose gradients), and equilibrium centrifugation (in ethidium bromide/CsCl solution). The purified cellular DNA, which was isolated from the cells late after infection, contained 0.006% free viral DNA. However, this cellular DNA contained about 2% integrated simian virus 40 DNA. As determined by DNA-DNA reassociation kinetics, this corresponds to approximately 20,000 integrated virus genome equivalents/cell. One day after infection, integration of the simian virus 40 DNA into cellular DNA was detected. This integration increased with the increase in the rate of synthesis of viral DNA. Replacement of 2% of host-specific by virus-specific nucleotide sequences in the cellular DNA of productively infected cells may cause alterations in the regulation of transcription and replication of the host cell genome that eventually result in cell death.

62. SIZE AND DISTRIBUTION OF SV 40 DNA SEQUENCES COVALENTLY LINKED WITH THE DNA OF PERMISSIVE MAMMALIAN CELLS.

Kuhn C, Waldeck W, Sauer G

Institut für Virusforschung, Deutsches Krebsforschungszentrum Heidelberg, Germany

Z Krebsforsch; 83(1):65-79 1975

Linear duplex DNA molecules consisting of covalently linked Simian virus 40(SV40)-host DNA sequences were isolated from SV40-infected CV-1 cells and characterized. CV-1 cell cultures were infected at a low multiplicity (0.5 plaque forming units/cell), labeled with 3Hthymidine (20 microCi/ml), and the DNA was selectively extracted. The DNA obtained from the NaCl-dodecyl-SO₄-supernatant was subjected to dye-buoyant-density CsCl-ethidium bromide equilibrium centrifugation; the light band containing relaxed circular and linear duplex DNA structures was used for further investigation of the viral-host DNA sequences. These molecules were isolated and purified by two successive cycles of DNA-DNA hybridization and elution steps using first CV-1 cell and then SV40-DNA immobilized on filters. In studies of the reassociation kinetics of this material, only part of the isolated DNA sequences (40%) was able to reassociate rapidly, while most of the DNA sequences reassociated slowly. This suggests the participation of various unique DNA sequences in formation of such viral-host DNA molecules. Treatment of the reassociated viral-host DNA sequences with single strand-specific S1 nuclease confirmed that unique host DNA sequences were always present near the viral DNA. Experiments with fragmented DNA molecules revealed an intimate association of repetitive CV-1 DNA with the SV40 DNA; the reiterated host DNA was confined to within the range of 800 bases from the viral sequences. The results suggest that most of the SV40 DNA sequences are probably integrated as fragments of subgenomic length. The results also suggest an arrangement of interspersed small repetitive sequences alternating with longer unique sequences within the CV-1 cell DNA. The author suggests that the presence of unique host DNA sequences within the purified viral-host DNA may reflect a higher degree of organization of the DNA of higher organisms.

63. SOME PROPERTIES OF SUPERHELICAL OLIGOMERIC AND INTEGRATED SV40 DNA SEQUENCES. (PP. 59-67)

Sauer G, Kuhn C, Kammer K, Waldeck W
Tumor Virus-Host Cell Interaction. Kolber A, ed. New York, Plenum Press, 1975.

Some properties of simian virus 40 (SV40) DNA sequences that are covalently linked with host cell DNA are discussed. Two situations are considered: (a) oligomeric SV40 DNA with integrated host DNA sequences; and (b) linear duplex DNA consisting of SV40-host DNA sequences in productively infected cells. Oligomeric SV40 DNA was isolated and purified, and the oligomers were immobilized, after denaturation, on filters and hybridized with either monomeric SV40 superhelical DNA or with host DNA in DNA-DNA hybridization reactions. There was a large discrepancy in base sequence homology between oligomers and monomeric SV40 DNA that cannot be explained by the presence, in host oligomeric SV40 DNA molecules, of host DNA sequences capable of hybridizing under these conditions. It is concluded that oligomeric SV40 DNA must contain approximately 15% of unique host DNA sequences incapable of hybridizing either with monomeric SV40 DNA or with repetitive host DNA. Integration of SV40 DNA sequences into host DNA during productive infection is a regular event that is independent of the multiplicities of infection. Substantial amounts of viral DNA sequences occur in the form of covalently linked viral-host DNA sequences. SV40 DNA sequences are particularly enriched in small DNA duplex molecules contained in the Hirt supernatant after selective extraction of the DNA at the end of the productive cycle. Integration also takes place in the macromolecular host DNA, but to a much lesser extent. Data from ultrasonic treatment and alkaline velocity sedimentation of material recovered from the light band of the Hirt supernatant (before and after hybridization to and elution from SV40 and CV-1 DNA) led to the following conclusion: within the range of 800 bases the integration site in mammalian DNA in these particular molecules must consist of reiterated host DNA sequences that are either directly adjacent to the viral DNA sequences or separated by only a few unique base sequences from the integrated viral sections.

64. CHARACTERIZATION OF SUPERCOILED OLIGOMERIC SV40 DNA MOLECULES IN PRODUCTIVELY INFECTED CELLS.

Martin MA, Howley PM, Byrne JC, Garon CF
Natl. Inst. Allergy and Infectious Diseases, Natl. Insts. Health, Bethesda, MD 20014
Virology; 71(1):28-40 1976

Oligomeric supercoiled forms of simian virus 40 (SV40) DNA, which appear during the latter stages of productive infection and account for more than 10% of the intracellular viral DNA 70 hr after infection, were characterized. The sedimentation constants of oligomeric DNA under neutral and alkaline conditions and the electrophoretic mobilities of the different supercoiled forms were determined. Nucleic acid hybridization studies as well as cleavage with bacterial restriction endonucleases indicated that oligomeric supercoiled DNA molecules contain only SV40 DNA sequences. These unintegrated viral DNA forms appeared predominantly in the Hirt pellet and sedimented in regions of alkaline sucrose gradients characteristic of high molecular weight cellular DNA.

65. FACTORS AFFECTING THE PROCESS AND EXTENT OF INTEGRATION OF THE VIRAL GENOME. (PP. 325-333)

Hirai K, Defendi V
Tumor Viruses Cold Spring Harbor Symposia on Quantitative Biology. Cold Spring Harbor Laboratory (Cold Spring Harbor, NY, (39), 1975.

The integration of viral DNA in transformed and tumor cells and the factors that modify the level of integration were investigated. Three cell lines were selected, SV3T3 T² and two Chinese hamster (CH) clones. Simian virus 40 (SV40) genomes were detected in SV40-transformed and tumor cells by DNA-RNA hybridization experiments. The amount of SV40 genome equivalents/diploid cells was assessed by DNA-DNA reassociation kinetics. Immunofluorescence was used in assaying SV40 T and V antigen. The number of genome equivalents/diploid cells varied between 1 and 20, with no particular distribution according to species. These data seem to imply multiple integration sites. The integrated viral genome was tested for stability by culturing two CH cell clones, one with a low number (1) of genome equivalents and one with a high number (20), over a long period of time. A split ratio of 1/10 was maintained for each culture passage. Over 10⁷ generations, the amount of viral DNA remained essentially stable in both cell lines. However, when the culture was enriched and the split ratio was raised, the amount of viral DNA decreased progressively. In determining the factors that affect integration, confluent monolayers of CH cells were subcultured, infected with SV40 (multiplicity, 20-50 plaque-forming units/cell) for 2 hr and placed in fresh medium in the presence of varying quantities of FCS. Viral DNA integration, cloning efficiency, and transformation frequency were tested. Pulse labeling after infection revealed a proportional percentage of labeled cells to the concentration of FCS in both infected and noninfected cultures. Cloning efficiency was not affected, but the transformation frequency increased dramatically between 1% and 5% FCS. Cytosine arabinoside did not affect the level of integration. (39 refs)

66. THE INTEGRATED STATE OF VIRAL DNA IN SV40-TRANSFORMED CELLS (MEETING ABSTRACT).

Sambrook J, Srinivasan PR, Dulbecco R
Salk Inst. Biol. Studies, San Diego, Calif.
Proc Natl Acad Sci USA; 60(4):1288-1295 1968

DNA preparations isolated from SV 3T3 and Py 3T3 cells were hybridized with RNA made in vitro with SV40 DNA as template. The degree of hybridization of SV 3T3 DNA, compared to that of Py 3T3 DNA, was equivalent to 20 SV40 genomes/cell. These studies eliminated the possibility that viral DNA in SV 3T3 cells is in the form of supercoiled circles of any size, and that it is in a free form of any configuration of molecular wt comparable to the DNA of the virion. (A. O. Deeney)

67. 'INTEGRATION' OF POLYOMA VIRUS DNA INTO MAMMALIAN GENOMES.

Babiuk LA, Hudson JB
Dep. Microbiology, Univ. British Columbia, Vancouver 8, British Columbia, Canada
Biochem Biophys Res Commun; 47(1):111-118 1972

Integration is defined as the ability of viral DNA to associate with cellular DNA in an alkali-stable linkage. The integration of Polyoma DNA in the genomes of mouse cells, hamster BHK-21 cells, and human Hep-2 cells was examined. The cells were infected with Polyoma virus, and the high mol wt cellular DNA was isolated at various times after infection by alkaline sucrose gradient sedimentation. The amount of integration was similar in the BHK and mouse cultures; the human cells demonstrated a much smaller level of integration,

possibly due to a relatively small degree of virus uptake. Following the initiation of viral DNA replication, the amount of viral DNA associated with mouse and hamster DNA increased notably. In the mouse cells approx 50% of the newly synthesized Polyoma DNA became associated with the cellular DNA. In two control experiments in which labeled or unlabeled Polyoma DNA was mixed with uninfected BHK-21 cells and layered onto alkaline sucrose gradients, approx 12% of the viral DNA became associated with the cellular DNA. The extent of integration was found to be dependent on the dose of inoculating virus. More integration was detected with higher doses of virus in both mouse and BHK-21 cells, however, the increase of integration was less than proportional at higher doses, suggesting that there may be a limited number of integration sites. The results support the hypothesis that Polyoma viral DNA becomes integrated into cellular DNA during the normal course of infection in mouse and BHK-21 cells. (16 Refs)

68. INTERACTIONS OF POLYOMA AND MOUSE DNAs. IV. TIME COURSE AND EXTENT OF INTEGRATION OF POLYOMA DNA INTO MOUSE DNA DURING LYTIC INFECTION.

Turler H

Dept. Molecular Biology, Univ. Geneva, 1211 Geneva 4, Switzerland

J Virol; 23(2):272-285 1977

The time course of covalent binding of polyoma viral DNA to mouse DNA was followed in mouse embryo cells that had been grown prior to infection in the presence of 5-bromodeoxyuridine. Density-labeled (HL) mouse DNA was separated from free polyoma DNA by CsCl isopycnic centrifugation. Polyoma DNA sequences present in HL mouse DNA were detected by hybridization with radioactive complementary RNA (cRNA) synthesized *in vitro*. In reconstruction experiments, the limit of detection was found to be, on the average, about 0.5 genome equivalent (ge) of polyoma DNA per cell. To find conditions for the isolation of HL mouse DNA and for its complete separation from free polyoma DNA, cultures infected at 4°C were used. HL mouse DNA extracted with sodium dodecyl sulfate and high salt concentrations (5 to 6 M CsCl) and then purified by three consecutive CsCl density gradient centrifugations was free from detectable amounts of polyoma DNA, whereas HL mouse DNA extracted with chloroform and phenol and purified in the same way always contained contaminating, noncovalently bound polyoma DNA. In lytically infected bromodeoxyuridine-prelabeled mouse embryo cultures, polyoma DNA bound to HL mouse DNA that had been extracted by the sodium dodecyl sulfate-CsCl procedure was first detected in small amounts (1 to 2 ge per cell) at 10 hr after infection. In cultures incubated with medium containing thymidine (5 µg/ml), 4 to 6 ge of polyoma DNA per cell was detected at 14 and 18 hr after infection. In these samples, practically all viral DNA was bound to high-molecular-wt HL mouse DNA. In cultures incubated with normal medium (no additions) and extracted between 17 and 20 hr after infection, 20 to 350 ge of polyoma DNA/cell banded with HL mouse DNA. However, when DNA of one of these samples was subfractionated by sodium dodecyl sulfate-salt precipitation prior to isolation of HL mouse DNA, about 80% of the viral DNA banding at increased density was present in the low-molecular-wt DNA fraction. This observation suggests that in normal medium some progeny viral DNA of increased density was synthesized. Covalent binding of polyoma DNA to density-labeled mouse DNA was demonstrated by alkaline CsCl density gradient centrifugation: nearly equal amounts of polyoma DNA were found in the H and L strands, respectively, as is expected for linear integration of viral DNA. The results lead to the conclusions that: early polyoma

messenger RNA (mRNA) is transcribed from free parental viral DNA; covalent linear integration is first detectable at the time when tumor (T)-antigen is synthesized; and only few copies (less than 10 ge/cell) become integrated between 10 and 18 hr after infection, i.e., during the period when cellular and viral DNA replication starts in individual cells. (Author abstract) (50 Refs)

C. Papovaviruses: Restriction Endonucleases and the Southern Gel-Filter Blotting Technique

69. CLEAVAGE OF INTEGRATED SV40 BY RI RESTRICTION ENDONUCLEASE.

Botchan M, McKenna G

Cold Spring Harbor Lab., Cold Spring Harbor, NY 11724

Cold Spring Harbor Symp Quant Biol; 38:391-395 1973

The association of host and viral DNAs was investigated using the restriction endonuclease EcoRI. Fragments resulting from EcoRI treatment of simian virus (SV)40-transformed mouse cells were detected by hybridizing radioactive RNA complementary (cRNA) to SV40 DNA to DNA extracted from each fraction of the DNA from the transformed cells and recovered by gel electrophoresis. The fraction of viral DNA represented by cRNA, the specific activity of the RNA, and the amount of DNA per cell showed that the mouse cell line SVT2 contained 1.6 SV40 genome equivalents per diploid cell and that the SV3T3 clone 9 contained 9.5 equivalents per diploid quantity of DNA. An experiment in which unlabeled Ad2+ND1 DNA was mixed with P32-labeled BALB-3T3 DNA, treated with EcoRI and analyzed by gel electrophoresis showed that it is possible to detect specific fragments of viral DNA in gels. Using the cleavage product of Ad2+ND1 as a marker, it was determined that the SV40-containing fragments had mol wt of 3.1×10^6 and 1.8×10^6 daltons, respectively. A covalent linkage between viral and chromosome DNA was implied by the fact that the sum of the mol wt of the two fragments was greater than the mol wt of the SV40 genome. The two bands contained 70% and 30% of the SV40 sequences, respectively. The fact that discrete bands were observed in the gel provides experimental evidence that in a clone of SV40-transformed cells, the viral DNA is integrated at a limited number of chromosomal sites. (41 Refs)

70. CHARACTERIZATION OF SV40 DNA RESCUED FROM TRANSFORMED MOUSE CELLS. (PP. 95-99)

Botchan M, Ozanne B, Sambrook J

Tumor Viruses Cold Spring Harbor Symposia on

Quantitative Biology. Cold Springs Harbor Laboratory (Cold Spring Harbor, NY, (39), 1975.

The mechanism and specificity of integration of viral DNA sequences were studied by characterizing the SV40 viral DNA rescued from SVT2 cells (BALB/c mouse embryo fibroblasts transformed by SV40). The rescued viral DNA from six different clones was treated with the restrictive endonucleases Hind II and III, and the fragments were separated by gel electrophoresis. DNA from SVT2 clones 3, 4, and 5 were indistinguishable from the wild-type SV40 strain. The SVT2-0 clone DNA contained two fragments (C and F), with a 150-nucleotide pair deletion in C and a 30-unit deletion in F. The SVT2-1 clone DNA contained a 60-unit deletion in fragment C and a 30-unit deletion in F. The deletions were concurrent but not in one contiguous region of the SV40 genome. Similar results were obtained with three different cell lines (SV3T3, MSV-SV101, and LS-SV101). The virus rescued from SVT2-0 transforms BALB/c 3T3 cells 500 times more efficiently than the wild type virus. This increased transformation efficiency was not a general property of rescued SV40 viruses. The SVT2 cells had only one complete copy of the viral genome; therefore, the recovery of different viral types must have occurred by processes subsequent to

initial insertion or transformation of cells with defective viral genomes. Various models for the creation of small deletions in viral DNA are discussed.

71. INTEGRATED SIMIAN VIRUS 40 SEQUENCES IN TRANSFORMED CELL DNA: ANALYSIS USING RESTRICTION ENDONUCLEASES (MEETING ABSTRACT).

Ketner G, Kelly TJ
Johns Hopkins Univ., Sch. Medicine, Baltimore, MD
21205
Proc Natl Acad Sci USA; 73(4):1102-1106 1976

The DNAs from five independent simian virus 40 (SV40) transformants of the BALB/c 3T3 mouse cell line were digested with either the HpaII or the BamHI restriction endonuclease, and the resulting fragments were fractionated by gel electrophoresis. The DNA fragments were denatured in situ in the gel and transferred to a membrane filter. Fragments containing viral DNA were detected by hybridization with high specific activity ³²P-labeled SV40 complementary RNA (cRNA) synthesized in vitro. Each of the lines yielded a small number of fragments containing SV40 DNA. The pattern of the fragments from each line was different. This finding indicated that the structure of the integrated SV40 DNA and/or its location in the host DNA are different in each line.

72. THE ARRANGEMENT OF SIMIAN VIRUS 40 SEQUENCES IN THE DNA OF TRANSFORMED CELLS.

Botchan M, Topp W, Sambrook J
Cold Spring Harbor Laboratory P.O. Box 100 Cold Spring Harbor, New York 11724
Cell (Camb); 9(2):269-287 1976

High molecular weight DNA, isolated from eleven cloned lines of rat cells independently transformed by SV40, was cleaved with various restriction endonucleases. The DNA was fractionated by electrophoresis through agarose gels, denatured in situ, transferred directly to sheets of nitrocellulose as described by Southern (1975), and hybridized to SV40 DNA labeled in vitro to high specific activity. The location of viral sequences among the fragments of transformed cell DNA was determined by autoradiography. The DNAs of seven of the cell lines contained viral sequences in fragments of many different sizes. The remaining four cell lines each contain a single insertion of viral DNA at a different chromosomal location. The junctions between viral and cellular sequences map at different places on the viral genome. (Author Abstract)

D. Papovaviruses: Establishment of Viral Genome in Germ Line - Karyotyping and Chromosome Analysis

73. ASSIGNMENT OF THE T-ANTIGEN GENE OF SIMIAN VIRUS 40 TO HUMAN CHROMOSOME C-7 (MEETING ABSTRACT).

Croce CM, Girardi AJ, Koprowski H
Wistar Inst. Anat. Biol., Philadelphia, Pa.
Proc Natl Acad Sci USA; 70(12):3617-3620 1973

Hybrid cell clones derived from mouse cells deficient in thymidine kinase (EC 2.7.1.21) and two different human cell lines transformed by simian virus 40 (SV40) and deficient in hypoxanthine phosphoribosyltransferase (EC 2.4.2.8) were examined for SV40 tumor (T) antigen (s). Concordant segregation of the gene(s) for SV40 T antigen and human chromosome C-7, was observed in these hybrids. The human chromosome C-7, which contains the gene(s) for SV40 T antigen, is preferentially retained by the majority of the hybrid clones tested. When hybrid clones positive and negative for SV40 T antigen, derived from the fusion of SV40-transformed Lesch-Nyhan fibroblasts with mouse cells, were fused with

CV-1 permissive cells, SV40-specific V antigen was observed only in the cultures derived from fusion of the hybrid clones positive for T antigen. This result indicates a linkage relationship between the human chromosome C-7, the SV40 T-antigen gene(s), and the SV40 genome(s) integrated in the human transformed cells.

74. SOMATIC CELL HYBRIDS BETWEEN MOUSE PERITONEAL MACROPHAGES AND SV40-TRANSFORMED HUMAN CELLS. I. POSITIVE CONTROL OF THE TRANSFORMED PHENOTYPE BY THE HUMAN CHROMOSOME 7 CARRYING THE SV40 GENOME.

Croce CM, Koprowski H
Wistar Inst. Anat. Biol., Philadelphia, Pa.
J Exp Med; 140(5):1221-1229 1974

Mouse peritoneal macrophages were hybridized with simian virus 40 (SV40)-transformed human cells, deficient in hypoxanthine guanine phosphoribosyltransferase (HGPRT) to demonstrate that the human chromosome 7, carrying the viral genome codes for "transforming factors" responsible for expression of the transformed phenotypic. Hybrid cells continued to proliferate in vitro with all the characteristics of transformed growth. Clones of these cells revealed, on karyological analysis, the universal presence of human chromosome 7 plus one or more other human chromosomes; most of the mouse chromosome sets were quasi-tetraploid. The retention of transformed growth characteristics in the hybrid cells and universal presence of chromosome 7 (sometimes the only human one in the hybrid karyotype) provided the evidence that the SV40 viral genome was incorporated into this particular chromosome. The fact that the human transforming genome had a dominant effect in progeny of somatic fusions between mouse and human heterokaryotypes suggests that fusions of this type may be used to identify viral genomes in other human cell lines.

75. GENETICS OF CELL TRANSFORMATION BY SIMIAN VIRUS 40. (PP. 335-343)

Croce CM, Huebner K, Girardi AJ, Koprowski H
Tumor Viruses Cold Spring Harbor Symposia on Quantitative Biology. vol. 39, Cold Spring Harbor Lab. (Cold Spring Harbor, NY, 1975).

A series of somatic cell hybrids between mouse cells and simian virus 40 (SV40)-transformed primate cells was studied for the expression of SV40 T antigen and tumor-specific transplantation antigen (TSTA) and for the rescuability of the SV40 genome. The purpose was to determine if the presence of the SV40-induced antigens in the hybrid cells was due to a specific chromosome in which the viral genome is integrated. The results indicated that integration of the SV40 genome into human chromosome 7 results in transformation of the human cells and in the expression of SV40-induced antigens. If integration of the SV40 genome in human chromosomes other than 7 ever occurred, it did not result in cell transformation and the expression of the virus-induced antigens. The expression of the SV40 T antigen in different monkey cells transformed by an adeno-7-SV40 hybrid was also related to a specific monkey chromosome; this chromosome resembles a human group C chromosome. Somatic cell hybrids between normal nondividing mouse cells and SV40-transformed human cells behaved as transformed cells and contained, without exception, the human chromosome 7 carrying the SV40 genome. Since no segregation into SV40 T antigen-negative hybrid clones was observed in these hybrids, it was concluded that the presence of the human chromosome 7 carrying the SV40 genome in the hybrids is mandatory for cell division. The human chromosome 7 apparently contains gene(s) that code for "transforming factors" responsible for the transformed phenotype.

76. INFECTION OF MOUSE BLASTOCYSTS WITH SV40 DNA: NORMAL DEVELOPMENT OF THE INFECTED EMBRYOS AND PERSISTENCE OF SV40-SPECIFIC DNA SEQUENCES IN THE ADULT ANIMALS. (PP. 375-380)

Jaenisch R

Tumor Viruses Cold Spring Harbor Symposia on Quantitative Biology. vol. 39, Cold Spring Harbor Lab. (Cold Spring Harbor, NY, 1975).

Preimplantation C3H inbred strain mouse blastocysts were infected with purified simian virus 40 (SV40) DNA by microinjection into the blastocoel. The infected embryos developed into mature and apparently healthy mice. Detection and measurement of SV40 sequences in DNA preparations from adult mouse tissues (liver, kidney, and brain) were accomplished by comparison of the reassociation kinetics of highly labeled, denatured SV40 DNA in the presence of DNA from experimental mice, control animals, or calf thymus. Molecular hybridization tests revealed the presence of SV40-specific sequences in some adult tissue. It was suggested that the viral DNA was integrated into the host genome at an early stage of development, but an extrachromosomal existence of the SV40 genome cannot be excluded. The mice were tumor-free at 1 yr of age; tumorigenesis may have required more time to occur. Testing for expression of an integrated viral genome in diverse differentiated tissues may provide a useful model system to study the regulation of differentiation.

77. ACTIVATION OF SV40 BY TRANSFER OF FRACTIONATED CHROMOSOMES FROM TRANSFORMED CELLS (MEETING ABSTRACT).

Shani M, Aloni Y, Huberman E, Sachs L

Dept. Genetics, Weizmann Inst. Science, Rehovot, Israel
Isr J Med Sci; 11(11):1214 1975

Metaphase chromosomes from an inducible SV40-transformed cell line with no observable infectious or free virus DNA were fractionated into four fractions and transferred into BSC1 cells, which permit SV40 virus multiplication. Chromatin material from all fractions was observed in the cytoplasm of the cells after chromosome transfer. Viral DNA sequences were found in three of the four fractions; infectious virus was activated in only two of the fractions. The smallest chromosomes did not contain either SV40 genomes susceptible to activation or integrated SV40 DNA sequences. The transfer of fractionated chromosomes may be useful for the activation and mapping of other genes. (no refs)

78. CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER CELLS TRANSFORMED BY SV40 VIRUS (MEETING ABSTRACT).

Nayar S

Dept. of Biology, Univ. of Chicago, Chicago, Ill. 60637
Proc Am Assoc Cancer Res; 17:135 1976

Incorporation of viral genome into host DNA has been implicated as a possible mechanism for cell transformation and virally-induced neoplasm. Using molecular hybridization technique, it was shown that about 6 viral genomes were integrated with the host DNA in SV40 infected MUT 295CL71 cells (C. Haas, et al, Proc Natl Acad Sci; 69:2160 1972). Whether or not such viral integration would manifest itself at cytogenetic level was studied by analyzing the karyotypic distribution of these cells. Chromosome preparations were made from colcemid treated cells arrested in mitosis at semiconfluency. Average number of chromosomes per cell was 22. About 25 generations after SV40 transformation, 42% of cells exhibited a chromosome number of 25 or more. Of this group of cells, a larger number exhibited hypertriploidy and hypertetraploidy. A number of other qualitative changes were also seen to occur in chromosomes.

These include, among others, chromatid aberrations, localized mostly to constitutive heterochromatin, chromosomal exchanges, micronucleation and chromosome pulverization. These quantitative and qualitative changes in chromosomes were persistent for nearly 45 generations and resemble those obtained by treatment with x-irradiation or alkylating agents. These cytogenetic data are consistent with the biochemical data obtained by Haas, et al above and suggest the possibility that chromosomal aberrations could be used as an index for virus-induced cell transformation. (Author Abstract)

E. Papovaviruses: Control of Integration and Excision of the Integrated Genome

79. USE OF VIRUSES FOR MEASURING THE TRANSFER OF HETEROGENEOUS FUNCTIONAL DNA FROM CELL TO CELL.

Melnick JL, Boyd AL, Butel JS

Baylor Coll. Med., Houston, Tex.

Bull Inst Pasteur; 71(4):397-427 1973

Three studies are discussed in which the method of DNA transfer was applied in order to introduce foreign DNA from mammalian cells into receptive heterologous cells. The first study on recovery of SV40 virus from transformed cells includes: (1) a review of the literature on general properties of SV40 transformed cells, including viral nucleic acids in transformed cells, viral antigens in transformed cells, and recovery of the transforming viral genome; (2) a general method for recovering the virus with the aid of "DNA transfer" and a method for obtaining SV40 from productive and nonproductive cell lines; and (3) the significance and four hypotheses for the mechanism by which integration of the viral genome is maintained. The second study deals with modifications occurring in hamster cells after incubation with DNA from simian cells. The choice of a system and adsorption of poliovirus by DNA-treated hamster cells are considered. This study demonstrated the possibility of transferring a functional DNA from simian cells to hamster cells in the presence of DEAE-dextran. The third study, formation of heterologous SV40 pseudovirus, includes a description of pseudovirions and incorporation of DNA from hamster cells into SV40 particles. Pseudovirion "sub-products" of a normal viral replicative cycle resemble the bacteriophage of "generalized transduction." Exogenous DNA may be encapsulated in SV40 particles, showing that the production and detection of heterologous pseudovirions may be possible. No biological activity has yet been demonstrated for heterologous pseudovirions. The method of DNA transfer is considered promising for passage of genetic information between mammalian cells. However, the usefulness of this method for transmission of genetic information between somatic cells is probably limited by a technical inability to locate numerous genetic markers in such systems. It is too early to form hypotheses concerning the relative merits of the 3 general approaches described and to attempt to predict which will ultimately be most useful.

80. INTEGRATION OF VIRAL INTO CHROMOSOMAL DEOXYRIBONUCLEIC ACID IN AN INDUCIBLE LINE OF POLYOMA-TRANSFORMED CELLS.

Manor H, Fogel M, Sachs L

Weizmann Inst. Sci., Rehovot, Israel

Virology; 53(1):174-185 1973

RNA-DNA hybridization has shown that in polyoma-transformed rat cells which can be induced to synthesize infectious virus (LPT cells) polyoma DNA sequences are associated with chromosomal DNA. RNA complementary to the viral RNA (cDNA) was synthesized in vitro, using purified viral DNA as a template and Escherichia coli RNA polymerase. High-molecular-weight chromosomal DNA was fractionated from linear and supercoiled viral DNA molecules

by centrifugation of whole cells through alkaline glycerol gradients. Hybridization carried out between the cRNA and fractionated chromosomal DNA showed that the amount of RNA hybridized to the LPT DNA was two to three times larger than the amount hybridized to DNA from normal rat cells. cRNA was also hybridized, under the same conditions, with mixtures containing a constant amount of normal cell DNA and varying quantities of purified viral DNA. These assays have established that a linear relationship exists between the amount of cRNA specifically hybridized with a given sample of DNA and the quantity of viral DNA in the sample. Using this relationship, it is estimated that LPT chromosomal DNA contains 6-9 genome-equivalents of polyoma DNA per cell. This quantity represents 18-29% of the amount of polyoma DNA found in the cells, as determined by hybridization of cRNA with unfractionated LPT DNA. To exclude the possibility that the chromosomally associated viral DNA is an artifact due to incomplete removal of the extrachromosomal viral DNA, control experiments were performed in which the cells were superinfected with polyoma virus (m.o.i. 500; 3 hr infection). In these experiments, less than 1% of the viral DNA introduced into the cells by the superinfecting virus were found by the same techniques to be associated with chromosomal DNA. Other experiments show that LPT cells do not contain significant amounts of complex viral DNA molecules which sediment in the vicinity of chromosomal DNA. It is therefore suggested that viral and chromosomal DNA are bound to each other by bonds which cannot be disrupted by alkali treatment.

81. RESCUE OF DEFECTIVE SV40 FROM MOUSE-HUMAN HYBRID CELLS CONTAINING HUMAN CHROMOSOME 7.

Croce CM, Huebner K, Girardi AJ, Koprowski H
Wistar Inst. Anat. Biol., Philadelphia, Pa.
Virology; 60(1):276-281 1974

Subcloning of simian virus 40 (SV40) T-antigen positive, V-antigen negative hybrid clones derived from the fusion of mouse thymidine kinase-deficient C1-ID cells and SV40-transformed human cells (LNSV) resulted in their segregation into T-antigen positive and negative subclones which still contained the full complement of mouse chromosomes. These subclones were analyzed for SV40 V-antigen and virion formation after fusion of the subclone cells with African green monkey kidney (CV-1) cells. All subclones which contained the human chromosome 7 showed the presence of V-antigen in the heterokaryocytes after fusion with CV-1 cells; all subclones which had lost human chromosome 7 failed to express V-antigen following fusion with CV-1 cells. Wild-type plaque-forming SV40 could not be rescued from any of the T-antigen positive, or negative clones or subclones, but defective SV40 virions were rescued from a hybrid subclone in which the only human chromosome present was chromosome 7; two subclones which had lost human chromosome 7 showed no SV40 virion formation. Thus, the SV40 genome appears to be integrated in human chromosome 7; if any part of the SV40 genome is integrated in other human chromosomes, it apparently cannot express any of its functions.

82. CHANGES OF REGULATION OF HOST DNA SYNTHESIS AND VIRAL DNA INTEGRATION IN SV40-INFECTED CELLS.

Hirai K, Campbell G, Defendi V
Wistar Inst. Anat. Biol., Philadelphia, Pa.
Cold Spring Harbor Conf Cell Proliferation; 1:151-165
1974

Previous studies on simian virus 40 (SV40)-infected Chinese hamster embryo cultures demonstrated an alteration

in control of DNA synthesis that was expressed in the appearance of polyploidy. The biological significance of polyploid cells was examined by monitoring (1) the fate of the viral genome and its relationship to host DNA, and (2) the degree of polyploidy in relation to the appearance of the transformed state. In SV40-infected Chinese hamster cells, induction of cell DNA synthesis and viral DNA integration showed a good concurrence in terms of order of appearance, dependence on the functioning viral genome and on culture conditions. However, viral DNA was integrated even when induction of cell DNA synthesis was abolished by drugs or by use of a lethal virus mutant. Thus, integration of viral DNA does not depend on replication of cell DNA and precedes, at least functionally, the induction of cell DNA synthesis. Reinitiation of cell DNA synthesis was demonstrated by the appearance of tetraploid metaphases at the time of first mitosis after infection and by the finding of heavy-heavy (HH) DNA when normal cycling through mitosis was inhibited. The total amount and the percentage of HH DNA (newly synthesized cell DNA) synthesized during the first 48 hr postinfection was directly proportional to the amount of integrated viral DNA. Chromosome analyses were performed on transformed colonies selected by the agar method and on transformed colonies selected by the morphological phenotype in monolayers. In both groups of colonies, the distribution of tetraploid frequency indicated that transformed colonies do not originate exclusively from infected, preexisting tetraploid cells. At a time when 30% of cells were T antigen-positive and 20% of metaphases were polyploid, an infected population was fractionated in an albumen gradient that separated cells on the basis of volume. Both polyploid cells and cells capable of producing transformed colonies were concentrated in the first two pooled fractions, which contained only a minority of the total cell population. Therefore, cell populations containing more tetraploid cells originate more transformed colonies than those containing few tetraploid cells. These results suggest that reinitiation of DNA synthesis may result from viral DNA integration, and that polyploid cells are the source of the transformed population.

83. ENHANCEMENT OF SIMIAN VIRUS 40 TRANSFORMATION AND INTEGRATION BY 4-NITROQUINOLINE 1-OXIDE.

Hirai K, Defendi V, Diamond L
Wistar Inst. Anat. Biol., Philadelphia, Pa.
Cancer Res; 34(2):3497-3500 1974

Chinese hamster embryo cells were treated with 4-nitroquinoline 1-oxide (4NQO) (0.4 microg/ml) for 2 hr prior to infection with simian virus 40 (SV40) and were subcultured 24 hr later to bring both treated and untreated cultures to the same density. After another 24 hr of incubation, the cell DNA was separated from the SV40 DNA and hybridized with SV40 complementary 3H-RNA. The number of "integrated" SV 40 genome equivalents (Eq)/diploid cell at 48 hr postinfection was greater in the 4NQO-treated cells than in the untreated SV40-infected cells. When 3H-thymidine was added to the 4NQO-treated cultures, there was no detectable synthesis of new SV40 DNA; thus, it is unlikely that 4NQO treatment rendered the nonpermissive cells permissive for viral DNA replication, thereby increasing the number of SV40 DNA molecules available for integration. RNA-DNA hybridization showed that 4NQO-pretreated cells was twice as high as the amount in the nuclei of untreated cells. 4NQO induced a 2- to 8-fold increase in SV40 transformation frequency, as determined by colony-forming efficiency in liquid medium. The increased number of genome Eq in 4NQO-treated cells is compatible with the hypothesis that the strand scission of cell DNA produced by 4NQO facilitates integration.

84. THE EFFECTS OF SERUM CONCENTRATION ON THE LEVEL OF INTEGRATION OF SIMIAN VIRUS (SV40) GENOME AND THE TRANSFORMATION FREQUENCY IN SV40-INFECTED CHINESE HAMSTER CELLS.

Hirai K, Defendi V
New York Univ. Medical Center, 550 First Ave., New York, NY 10016
Virology; 69(1):229-236 1976

Chinese hamster embryo cultures were treated with different serum concentrations during the first 48 hr after simian virus 40 (SV40) infection. The treatment modified the proportion of cells in DNA synthesis, the amount of SV40-DNA integrated, the proportion of cellular DNA with 5-bromodeoxyuridine substitution in both strands, the proportion of polyploid cells, and the transformation frequency. All these parameters increased in a coordinated way as function of the serum concentration. It is suggested that the increase in the number of cells recruited into DNA synthesis facilitates the integration of viral DNA with an increased probability of transformation.

85. SIMIAN VIRUS 40 IN SYNCHRONIZED MONKEY CELLS: INTEGRATION OF VIRAL DNA INTO THE CELL GENOME AND TIMING OF REPLICATION. (PP. 69-89)

Girard M, Manteuil S, Fisman M, Marx M, Danglot G
Tumor Virus-Host Cell Interaction. Kolber A, ed. New York, Plenum Press, 1975.

Experiments are reviewed in which CV1 monkey cells were synchronized, infected with SV40 at different times of mitosis, and the time course of viral DNA replication and of some of the early events of the virus growth cycle was determined to examine the relationship among the early events of the SV40 growth cycle, the initiation of viral DNA replication, and the timing of the host cell cycle periods. The results led to the conclusion that both SV40 and polyoma virus require the expression of a cellular function to initiate viral DNA replication in permissive cells. This function seems to be expressed by the cell only at the time of a G1-S interval. Pulse-labeling experiments with thermosensitive SV40 mutants, such as tsA30, have indicated that the gene product, thermolabile in the case of tsA30, is a diffusible factor specifically required to initiate replication on the viral chromosome. The thermolability of the tsA30 initiator protein is readily reversible but, in permissive conditions, synthesis of the new initiator molecules has to take place continuously in the infected cell to sustain the full rate of viral DNA replication. The integration of SV40 DNA into the chromosomal DNA of permissive cells during the lytic cycle was investigated in a series of reconstruction experiments. Both the time course of viral DNA replication and that of the appearance of viral DNA sequences in the high molecular weight DNA of the cell were determined. The amount of radioactive cRNA hybridized with the high molecular weight DNA molecules extracted from the infected CV1 cells more than doubled in the immediate hours following infection, dropped back to background levels after 6 hr, and then increased progressively until a plateau was reached at 16 hr. These results indicate that the integration of SV40 DNA into the host cell chromosome is an early event that precedes viral DNA synthesis and that integration does not seem to depend upon any particular stage of the cell cycle. It is not known whether integration of SV40 DNA into the DNA of the permissive cell might be an actual prerequisite to viral DNA replication.

86. THE STATE OF FREE VIRAL DNA IN RAT CELLS TRANSFORMED BY POLYOMA VIRUS (MEETING ABSTRACT).

Prasad I, Zouzas D, Basilico C
Dept. Pathology, New York Univ. Sch. Medicine, New York, NY 10016
J Cell Biol; 70(2/Part2):67a 1976

Infection of rat cells (F2408 line) with polyoma virus did not cause virus multiplication, but induced transformation. Transformed cells did not produce infectious virus, but virus was rescued from these cells after fusion with mouse cells. Transformed rat cells contained in addition to integrated viral genomes, 20-50 copies of non-integrated viral DNA equivalents per cell. Free viral DNA molecules were also found in cells transformed by the tsA and ts8 polyoma mutants and kept at 33°C. When tsA transformed rat cells were incubated at 40°C, free viral DNA molecules could not be detected. However, shift to the permissive temperature caused the induction of these molecules. The mitomycin C treatment of transformed cells increased the yield of free viral DNA molecules by 50-200 fold. Most of the free viral DNA molecules were supercoiled and found in the nuclei of the transformed cells. Their specific infectivity was about 100 fold lower than that of polyoma DNA extracted from productively infected cells. These results suggest that these molecules contain a large proportion of defectives.

87. REGULATION OF VIRAL TRANSCRIPTION AND TUMOR ANTIGEN EXPRESSION IN CELLS TRANSFORMED BY SIMIAN VIRUS 40.

Basilico C, Zouzas D
Department of Pathology, New York University School of Medicine, New York, N.Y. 10016
Proc Natl Acad Sci USA; 73(6):1931-1935 1976

We have studied the expression of simian virus 40 (SV40) specific tumor antigen (T-antigen) and viral RNA in SV40-transformed mouse 3T3 cells that are temperature-sensitive for the expression of the transformed phenotype (tsSV3T3). Although transformed by wild-type SV40, tsSV3T3 cells at 32 degrees behave like standard transformants, while at 39 degrees they became arrested in G1 after reaching saturation density or under conditions of serum starvation. tsSV3T3 cells at 32 degrees or exponentially growing at 39 degrees are uniformly T-antigen positive. However, after G1 arrest at 39 degrees the majority of the cells becomes T-antigen negative. Induction of proliferation in the resting cultures results in the reappearance of T-antigen in most of the cells, concomitant with the induction of DNA synthesis. The reason for the disappearance of T-antigen from tsSV3T3 cells arrested in G1 seems to reside in a transcriptional control operating on the integrated viral DNA, since these cells contain no appreciable amounts of SV40 specific RNA. Viral RNA can be easily detected in cells growing at 32 degrees or at 39 degrees. The results suggest that transcription of the viral genome in SV40-transformed cells is cell-cycle-dependent. (Author Abstract)

88. POLYOMA GENOME IN HAMSTER BHK-21-C13 CELLS: INTEGRATION INTO CELLULAR DNA AND INDUCTION OF THE VIRAL REPLICON.

Folk WR, Bancuk JE
Department of Biological Chemistry, The University of Michigan Medical School, Ann Arbor, Michigan 48109
J Virol; 20(1):133-141 1976

When grown at 39.5 degrees C, BHK-21-C13 cells transformed by A gene mutants of polyoma virus contain viral sequences that are predominantly associated with cellular DNA pelleted in the Hirt lysis procedure. At this temperature, in cells that are inducible for viral DNA replication (Folk, 1973), the majority of the viral genomes are covalently joined

with cellular DNAs containing repetitious sequences. Upon a shift to 31 degrees C, free viral genomes appear and are replicated. Coupled with the replication of the free viral genomes at 31 degrees C is an increase in the viral genomes associated with cellular DNA. (Author Abstract)

89. STATE OF THE VIRAL DNA IN RAT CELLS TRANSFORMED BY POLYOMA VIRUS. I. VIRUS RESCUE AND THE PRESENCE OF NONINTEGRATED VIRAL DNA MOLECULES.

Prasad I, Zouzas D, Basilico C

New York Univ. Sch. Medicine, New York, NY 10016
J Virol; 18(2):436-444 1976

When polyoma virus was interacted with a continuous line of rat cells, the infection did not cause virus multiplication but induced transformation. Transformed cells did not produce infectious virus, although in all clones tested virus could be rescued upon fusion with permissive mouse cells. Transformed rat cells contained, in addition to integrated viral genomes, 20 to 50 copies of nonintegrated viral DNA equivalents per cell (average). Nonintegrated viral DNA molecules were also found in cells transformed by the ts-a and ts-8 polyoma mutants and maintained at 33 C. These "free" viral DNA particles were not due to a virus carrier state, because the number of nonintegrated viral DNA molecules was unchanged when cells were grown in antipolyoma serum. Recloning of the transformed cell lines produced subclones, which also contained free viral DNA. Most of these molecules were supercoiled and were found in the nuclei of the transformed cells. The nonintegrated viral DNA is infectious; that its specific infectivity is about 100-fold lower than that of polyoma DNA extracted from productively infected cells suggests that these molecules contain a large proportion of defectives. This free viral DNA may have originated from an integrated template.

90. EXCISION OF VIRAL DNA FROM HOST CELL DNA AFTER INDUCTION OF SIMIAN VIRUS 40-TRANSFORMED HAMSTER CELLS.

Rakusanova T, Kaplan JC, Smales WP, Black PH
Massachusetts General Hosp., Boston, MA 02114
J Virol; 19(1):279-285 1976

Viral DNA is covalently linked to cellular DNA in transformed cells. The authors demonstrate that the simian virus 40 (SV40) genome is excised from its integrated state prior to viral replication. They used SV40-transformed inbred hamster kidney cells and sucrose gradient velocity sedimentation techniques to show that the SV40 DNA is linked to cellular DNA by alkali-stable bonds. The Hirt extraction procedure was employed to measure the excision of viral DNA following viral stimulation with either mitomycin C or irradiation. This method follows the movement of DNA from a high molecular wt host cell DNA to a pool of low molecular wt DNA. The authors demonstrate that the increase in the low molecular wt DNA fractions is not due to random breakage of cellular DNA. Using irradiation and treatment with cytosine arabinoside, an inhibitor of DNA replication, the authors show that excision of SV40 DNA may have preceded viral DNA replication by approximately 7 hr.

91. ISOLATION AND CHARACTERIZATION OF A HEAT-INDUCIBLE SIMIAN VIRUS 40 MUTANT.

Rothschild H, Lockwood MP

Department of Medicine, Louisiana State University,
School of Medicine, New Orleans, Louisiana 70112
J Virol; 19(2):374-381 1976

We have isolated a new type of temperature-sensitive mutant of simian virus 40 (SV40) that is capable of productive infection in permissive cells but not of maintenance of viral DNA integration in transformed cells at the conditional

temperature. Virus development is induced when cells transformed by this mutant are shifted to temperatures above 39 degrees C, but it is not induced below this temperature. The plaque-purified, temperature-sensitive mutant virus confers heat inducibility to new host cells, indicating that the conditional function is a property of the viral genome. Unlike previously described temperature-sensitive SV40 mutants, in(ts)-1501 is capable of productive infection in permissive cells at the conditional temperature. The morphology, growth, and oncogenicity of in(ts)-1501-transformed cells at 37 degrees C are similar to those of cell lines transformed by wild-type SV40. HK10-c2(in(ts)-1501), a cloned cell line, transformed at 37 degrees C by the mutant virus, exhibits a transient increase in DNA synthesis before cell death at the conditional temperature. Many properties of in(ts)-1501 are analogous to those of the heat-inducible mutants of bacteriophages in which a heat-inactivated protein is responsible for the stable integration of the prophage in the bacterial chromosome. (Author Abstract)

F. Papovaviruses: Virus-Cell Hybrid Genomes as Possible Consequences of Integration

92. ACQUISITION OF SEQUENCES HOMOLOGOUS TO HOST DEOXYRIBONUCLEIC ACID BY CLOSED CIRCULAR SIMIAN VIRUS 40 DEOXYRIBONUCLEIC ACID.

Lavi S, Winocour E

Weizmann Inst. Sci., Rehovot, Israel
J Virol; 9(2):309-316 1972

BS-C-1 African green monkey cells were infected at varying multiplicities of infection (MOI) with SV40. Viral closed circular DNA was extracted from infected cells and the ability of viral DNA to hybridize with host cell DNA was studied. It was found that the production of closed circular SV40 DNA homologous to host cell DNA depended on the MOI of SV40 infection. At low MOI (0.032 or 0.16 plaque-forming U (PFU)/cell), the proportion of viral DNA which hybridized with host DNA was low, while at high MOI (4-3,000 PFU/cell), the proportion of viral DNA which hybridized with host cell DNA increased as the MOI increased. The same MOI effect was seen when closed circular SV40 DNA was extracted from purified virions rather than from the infected cell complex. When BS-C-1 cells were infected at high MOI with plaque-purified SV40, none of the SV40 DNA in infected cells was homologous with host cell DNA. However, when undiluted plaque-purified SV40 that had been through several cell passages was used for infection, the production of viral DNA homologous to host cell DNA was restored.

93. THE EVOLUTION OF NEW SPECIES OF VIRAL DNA DURING SERIAL PASSAGE OF SIMIAN VIRUS 40 AT HIGH MULTIPLICITY.

Brockman WW, Lee TN, Nathans D

Johns Hopkins U. Sch. Med., Baltimore, Md.
Virology; 54(2):384-397 1973

Viral DNA isolated during serial undiluted passage of SV40 was analysed by electrophoresis of fragments produced by H influenzae restriction endonuclease and by DNA-DNA hybridization. Compared to parental SV40 DNA, early passage DNA showed alterations at many sites in the population of DNA molecules, although certain sites were more frequently altered than others as evidenced by the reduced yield of some original DNA fragments and the appearance of new fragments. With continued passage, new dominant species of viral DNA evolved which yielded simple restriction endonuclease digest patterns. DNA molecules from all passages retained SV40 DNA sequences; however, the percentage of total DNA sequences which corresponded to SV40 sequences diminished to about 30% or less in late

passage DNA. Repetitive host cell DNA sequences were detected in a high percentage of late passage DNA molecules, but accounted for 20% or less of total sequences present. Therefore the new species of viral DNA which evolved probably contain predominantly nonrepetitive host DNA sequences. The primary events in the mechanism producing this new species probably consist in the recombination between or within SV40 DNA molecules or between SV40 and host DNA, the latter representing integration and mis-excision of viral DNA. In addition, errors of DNA replication may give rise to duplication or deletion of segments. Once a primary change has occurred, selection of the most rapidly replicating molecules might then ensue.

94. ACQUISITION OF SEQUENCES HOMOLOGOUS TO HOST DNA BY CLOSED CIRCULAR SIMIAN VIRUS 40 DNA. II. FURTHER STUDIES ON THE SERIAL PASSAGE OF VIRUS CLONES.

Lavi S, Rozenblatt S, Singer MF, Winocour E
Dept. Genetics, Weizmann Inst. Science, Rehovot, Israel
J Virol: 12(3):492-500 1973

The results of the serial passage of three plaque isolates of simian virus 40 (SV40) strain 777 and one plaque isolate of strain 776 in monkey BS-C-1 cells are reported. With all four plaque isolates, serial passage resulted in the accumulation of closed circular SV40 DNA molecules containing covalently linked sequences homologous to reiterated host cell DNA. The percentage of viral DNA which hybridized to host DNA at a given passage varied widely in the different sets of serial passages. Fractionation of the closed circular SV40 DNA molecules on alkaline sucrose gradients showed that the substituted virus DNA was smaller in size than the DNA of plaque-purified virus and that it was defective with respect to plaque-forming ability. The presence of host sequences in replicative forms of the viral DNA and the incorporation of H³-thymidine into host sequences isolated from the mature substituted virus DNA molecule showed that the substituted SV40 DNA was capable of replication under the conditions of undiluted serial passage. The results indicate that events which occur during an early passage may dictate the nature of the substituted viral progeny produced during subsequent passages. (21 Refs)

95. ACQUISITION OF SEQUENCES HOMOLOGOUS TO HOST DNA BY CLOSED CIRCULAR SIMIAN VIRUS 40 DNA. III. HOST SEQUENCES.

Rozenblatt S, Lavi S, Singer MF, Winocour E
Dept. Genetics, Weizmann Inst. Science, Rehovot, Israel
J Virol: 12(3):501-510 1973

Serially passaged simian virus 40 (SV40) DNA, in which at least 66% of the molecules contained covalently linked cellular DNA sequences was isolated from cultures of infected monkey BS-C-1 cells. The preparation was then digested to completion with *Hemophilus influenza* restriction endonuclease. Polyacrylamide gel electrophoresis of the resultant fragments revealed nine distinct peaks. Peaks 3 and 4 were doublets, each containing two classes of fragments which differed only slightly in their electrophoretic mobilities. The fragments were found to differ electrophoretically from those produced by the action of the same enzyme on plaque-purified virus DNA. DNA-DNA hybridization analysis of the cleavage products showed the presence of highly reiterated cell DNA sequences in two of the nine classes of fragments. One of these classes did not appear to arise from every substituted molecule, and the second class hybridized with extremely high efficiency to cell DNA and was virtually free of SV40 sequences. A third class of fragments showed no detectable hybridization with filters containing cell DNA and hybridized poorly with filters containing plaque-purified virus DNA. However, they hybridized with high efficiency to filters

containing the same serially passaged virus DNA from which they were originally obtained. This hybridization pattern indicated the presence of cell DNA sequences too unique to register in the direct hybridization reaction with cell DNA immobilized on the filter. It was estimated that 27.4% of the sequences in the SV40-substituted DNA molecules were host sequences. The majority were considered to be of the nonreiterated type. (13 Refs)

96. THE HOST DNA SEQUENCES IN DIFFERENT POPULATIONS OF SERIALY PASSED SV40.

Frenkel N, Lavi S, Winocour E
Dept. Genetics, Weizmann Inst. Sci., Rehovot, Israel
Virology: 60(1):9-20 1974

The closed-circular simian virus 40 (SV40) DNA which evolved during four independent sets of high-multiplicity serial passages of plaque-purified virus stocks in monkey BS-C-1 cells was studied by reassociation kinetics. The results indicate that the host DNA sequences covalently linked to viral sequences in such serially passaged SV40 DNA are predominantly of the nonreiterated type. They are similar in populations evolving during a given set of serial passages and can be different in populations arising during different sets of serial passages starting from the same plaque isolate. They do not represent a random selection of the total sequences present in the host cell genome. The data indicate that either the number of primary recombination sites on the cellular genome is very limited, or the number of such sites is large but only a few of the initial recombination products replicate preferentially.

G. Papovaviruses: Co-Transcription of Linked Viral and Host DNA Sequences

97. SV40-SPECIFIC RNA IN THE NUCLEUS AND POLYRIBOSOMES OF TRANSFORMED CELLS (MEETING ABSTRACT).

Lindberg U, Darnell JE
Albert Einstein Coll. Med., New York, N. Y.
Proc Natl Acad Sci USA: 65(4):1089-1096 1970

Heterogeneous nuclear RNA and polysomal RNA of cells transformed by the oncogenic virus SV40 are analyzed. Nuclear molecules containing virus-specific sequences were considerably longer than presumed virus-specific mRNA molecules from cytoplasmic polyribosomes. Results showed that there were nuclear molecules greater than 4×10^6 and polysomal molecules less than 1.7×10^6 that contained RNA sequences complementary to SV40 DNA. These findings suggest the possibility that cytoplasmic mRNA is derived by the specific cleavage of larger nuclear RNA.

98. PRESENCE OF CELL AND VIRUS SPECIFIC SEQUENCES IN THE SAME MOLECULES OF NUCLEAR RNA FROM VIRUS TRANSFORMED CELLS.

Wall R, Darnell JE
Dept. Biol. Sci., Columbia U., New York, N.Y.
Nature (Lond): 232(29):73-76 1971

The nuclear events involved in the production of polysomal mRNA in mammalian cells were investigated. Hybridization studies were carried out with 3T3, SV3T3 and BSC-1 mouse cells grown as monolayers to study the transcription of SV40 DNA in transformed cells. Hybridization conditions were used in which no molecular breakage occurred during incubation and specific hybrid formation could be achieved without the necessity of RNAase treatment. The hybridization of polysomal RNA from SV3T3 cells to SV40 DNA filters was 6 to 12 times better than to blank filters. When equivalent amounts of radioactive polysomal RNA from 3T3 cells were exposed to SV40 DNA, the amount of radioactivity bound was only slightly higher than that bound

to blank filters. The selection of virus-specific RNA appeared to be both dependent on SV40 DNA on the filters and specific for RNA from transformed cells. When undegraded polysomal RNA from SV3T3 and untransformed 3T3 cells was hybridized to 20gamma SV40 DNA filters for 8 hr in 30% formamide hybridization solution at 45 C, a substantial fraction of the SV3T3 polysomal RNA which was initially selected on SV40 DNA rehybridized to viral DNA. The viral DNA-selected polysomal mRNA from transformed cells was composed largely of SV40-specific sequences since 40% of the selected RNA hybridized back to SV40 DNA. Apparently, nuclear RNA in transformed cells contains both host- and virus-specific sequences.

99. TRANSCRIPTION OF SV40 IN LYTICALLY INFECTED AND TRANSFORMED CELLS. (PP. 91-116)

Sambrook J, Jackson A, Keller W, Ozanne B, Sharp PA, Sugden B

Tumor Virus-Host Cell Interaction. Kolber A, ed. New York, Plenum Press, 1975.

At the beginning of simian virus 40 (SV40) DNA replication in monkey cells there is an increase in viral RNA synthesis and a change in transcription. At least some control of virus gene expression is exerted at the level of RNA. All of the early functions of SV40 were shown to be coded by the E or (-) strand of the SV40 DNA (that complementary to cRNA) and the late viral functions by the L or (+) strand. There is at least one strand switch during transcription of late SV40 RNA. To determine the characteristics of SV40-specific transcription, the ability of RNA to hybridize to SV40 DNA was tested. In monkey cells late in SV40 infection, it was host polymerase II that transcribed the viral DNA; the same enzyme was probably responsible for synthesis of both early and late sequences of viral RNA. Early and late regions of the viral genome were mapped. It was assumed that early RNA is transcribed from a contiguous portion of the viral genome. All the early functions of SV40 were located within fragments A and C; all sequences of B and D and part of A and C code for late functions. If all early genes of SV40 are contiguous, strand switches between early and late RNA's occur at positions 55 and 24. Explanations for viral regulation and for the mechanism of the shift from early to late RNA synthesis are offered. Separated strands of SV40 DNA were used to measure the percentage of viral genome transcribed into RNA in mouse SV40 transformants and other cell lines, and the positions of these sequences were mapped. Nearly all transformed cell lines contained RNA complementary to more sequences of E strand DNA than did lytically infected cells. Three premises are used to account for viral RNA synthesis in transformed cells: (a) SV40 DNA integrates into host DNA with a break in its late genes, (b) integration does not necessarily occur at the same site within the viral genome in different cell lines, and (c) integration places viral DNA under the control of host promoter(s). The model indicates that after initiating transcription at a host promoter, the RNA polymerase enters the integrated viral DNA on the E strand in the late region of the genome. It continues along SV40 sequences, synthesizing first "anti-late" and then early RNA, before termination occurs at the 3' end of the early genes.

100. EVIDENCE FOR SV40 SPECIFIC RNA CONTAINING VIRUS AND HOST SPECIFIC SEQUENCES (LETTER TO EDITOR).

Jaenisch R

Dept. Biochemistry, Princeton Univ., Princeton, NJ 08540
Nature; 235:46-47 1972

An attempt was made to characterize the nature of the different simian virus 40 (SV40) RNA species found after lytic infection of monkey cells and to explain the occurrence of a large heterogeneous SV40-specific RNA species which is larger

than the monomeric SV40 DNA molecule. Confluent cultures of secondary African green monkey cells were infected with SV40 and 2 hr later 0.2 milliCi of P32 added. At 40 hr after infection, 1 milliCi 3H-uridine was added for 2 hr and then the cells were harvested. The RNA was extracted and analyzed by polyacrylamide gel electrophoresis. The P32 radioactivity appeared in peaks corresponding to 28Svedberg (S) and 18S RNA and the H3 radioactivity was found in peaks corresponding to 32S and 45S RNA. Two main peaks of hybridizable counts had mol wt of 6.5×10^6 and 1×10^6 and migrated between 28S and 18S ribosomal RNA. In addition, a large heterogeneous virus-specific RNA with a mol wt of $1.5-3 \times 10^6$ was detected. The small species of SV40 RNA appeared to contain predominantly SV40-specific sequences, while the larger species of RNA contained both virus-specific and non-virus-specific sequences. The large heterogeneous class of RNA may have been transcribed from a template that contained both viral and cellular DNA.

101. COVALENTLY LINKED CELL AND SV40-SPECIFIC SEQUENCES IN AN RNA FROM PRODUCTIVELY INFECTED CELLS.

Rozenblatt S, Winocour E

Dept. Genetics, Weizmann Inst. Science, Rehovot, Israel
Virology; 50:558-566 1972

High mol wt (HMW) simian virus 40 (SV40)-specific RNA molecules, whose size exceeded that of a single strand of viral DNA, were detected in the nuclei of productively infected monkey BS-C-1 cells. Sedimentation through a deuterated dimethylsulfoxide-sucrose gradient indicated that the HMW SV40 RNA species had a mol wt in the range of 1.9×10^6 to 10×10^6 daltons. Compared with a single strand of SV40, mol wt 1.7×10^6 daltons, the HMW SV40 RNA was considerably larger. Hybridization studies showed that the HMW SV40 RNA contained host-specific consequences covalently linked to virus-specific sequences. The proportion of host-specific sequences appeared to exceed that of viral sequences in these molecules. It was concluded that at least some of the HMW viral RNA resulted from the co-transcription during lysis of integrated viral DNA and adjacent cellular DNA. (20 Refs)

III. TECHNIQUES FOR THE STUDY OF THE INTEGRATED ADENOVIRUS GENOME

A. Adenoviruses: Resolution of the Integrated Genome by Centrifugation Techniques

102. INTEGRATION OF THE DEOXYRIBONUCLEIC ACID OF ADENOVIRUS TYPE 12 INTO THE DEOXYRIBONUCLEIC ACID OF BABY HAMSTER KIDNEY CELLS.

Doerfler W

Rockefeller U., New York, N.Y.

J Virol; 6(5):652-666 1970

This study demonstrates the integration of viral DNA of adenovirus type 12 (Ad12) into cellular DNA of baby hamster kidney cells though covalent linkage. Adsorption of 3H-Ad12 to baby hamster kidney cells occurred more efficiently at low concentrations with release of 82% of the 3H activity that was cell associated being recovered in the medium at the end of 2 hr. The parental viral label hybridized predominantly to viral DNA and later to cellular DNA with a 25 to 1,380-fold higher value in infected cells as compared to uninfected control cells. Integration values are calculated to be 5-55 Ad12 DNA equivalents per cell, with only slightly lower values in the presence of cytosine arabinoside, cycloheximide and actinomycin D, indicating that DNA replication is not necessary for integration to occur.

103. THREE SIZE-CLASSES OF INTRACELLULAR ADENOVIRUS DEOXYRIBONUCLEIC ACID.

Burlingham BT, Doerfler W
Dept. Cell Biol., Sch. Med. U. Maryland, Baltimore
J Virol; 7(6):707-719 1971

Productive or nonproductive infection of KB cells by human adenovirus 12 (Ad 12) strain Huie or Ad 2 strain adenoid 6 resulted in the synthesis of 3 classes of viral DNA: a class which sedimented in alkaline sucrose gradients greater than 45S; a species which sedimented with DNA extracted from infectious adenovirions; and a class which sedimented at 18S. Purified adenovirions with 3H-labeled DNA as inoculum permitted the fate of the parental adenovirus DNA to be followed; more than 90% of the label incorporated into the cells was acid precipitable. The fast-sedimenting class of adenovirus DNA that varied between 45-80S (probably due to mechanical breakage of cellular DNA) specifically hybridized with the viral RNA. The hybridization to cellular DNA was variable and ranged from 0.1-5%. Control experiments with recovery of added 14C-Ad DNA indicated that the fast-sedimenting label from infected cells was comprised of viral genetic material; the complete sensitivity of this material to deoxyribonuclease treatment suggested that this class DNA is uncoated within the cell. An adenovirus DNA which cosedimented with Ad 12 marker DNA also sedimented at 33S in alkaline sucrose gradients and at 29S (34S and 32S for Ad2-DNA) in neutral sucrose gradients; this DNA underwent hybridization only to viral DNA and not to cellular DNA. Essentially all of this class of adenovirus DNA was susceptible to deoxyribonuclease, which indicated that it too was uncoated. The slow-sedimenting DNA also hybridized only to viral DNA and was sensitive to deoxyribonuclease. Correlation of the amounts of label in each DNA class with time indicated that the parental Ad 2 or Ad 12 DNA is cleaved into 18S fragments which may become linked to the fast-sedimenting cellular DNA and serve as precursors to the integrated form of Ad DNA. Inhibition of macromolecular synthesis with thymidine, actinomycin D or cycloheximide had little effect on the formation of the slowly sedimenting species of viral DNA. These results suggest that the 18S viral DNA is not synthesized but is formed by an endonuclease within the cell or the adenovirion.

104. INTEGRATION OF ADENOVIRUS DNA INTO THE CELLULAR GENOME. (PP. 505-521)

Doerfler W, Burger H, Ortin J, Fanning E, Brown DT, Westphal M, Winterhoff U, Weiser B, Schick J
Tumor Viruses Cold Spring Harbor Symposia on
Quantitative Biology, vol. 39, Cold Spring Harbor Lab.
(Cold Spring Harbor, NY, 1975).

The results from two different experimental systems concerning the integration of adenovirus (Ad) DNA into the cellular genome are presented. KB cells productively infected with Ad2 contain a fast-sedimenting form of viral DNA (50S-90S) that is stable in alkali; this represents viral DNA integrated into the host DNA. Reassociation experiments suggest that about 2,000-5,000 viral DNA copies per cell exist in the fast-sedimenting form. The 50S-90S DNA does not reanneal appreciably with itself. After the purified viral DNA was extracted from purified Ad2 virions, circular forms of viral DNA were seen by electron microscopy; these circles represent the total genome or one-quarter of the viral genome. These circles may serve as intermediates in the integration process. The transcription kinetics of Ad12 DNA in abortively infected BHK21 cells was determined. RNA molecules are found that sediment at 25S and at 35S in sucrose density gradients; viral RNA of high molecular weight may be transcribed from integrated viral sequences. There are palindromic sequences in the Ad2 genome; these palindromes

may serve as viral counterparts of repetitive or palindromic sequences in mammalian DNA that may serve as the recognition system required for integration.

105. INTRACELLULAR FORMS OF ADENOVIRUS DNA. III. INTEGRATION OF THE DNA OF ADENOVIRUS TYPE 2 INTO HOST DNA IN PRODUCTIVELY INFECTED CELLS.

Burger H, Doerfler W
Inst. Genetics, U. Cologne, W. Germany
J Virol; 13(5):975-992 1974

KB cells productively infected with human adenovirus type 2 contain an alkali-stable class of viral DNA sedimenting in a broad zone between 50-90S as compared to 34S for virion DNA. This type of DNA was characterized as viral by DNA-DNA hybridization. It is extremely sensitive to shear fragmentation. Extensive control experiments demonstrated that the fast-sedimenting viral DNA is not due to an artifactual drag of virus DNA mechanically trapped in cellular DNA or to association of viral DNA with protein or RNA. Furthermore, the fast-sedimenting DNA is found after infection with multiplicities between 1-1000 plaqueforming U/cell and from 6-8 hr post-infection until very late in infection (24 hr). Analysis in dye-bouyant density gradients eliminated the possibility that the fast-sedimenting viral DNA represents supercoiled circular molecules. Upon equilibrium centrifugation in alkaline CsCl density gradients, the fast-sedimenting viral DNA banded in a density stratum intermediate between that of cellular and viral DNA. In contrast, the 34S virion DNA, isolated and treated in the same manner as the fast-sedimenting DNA, cobanded with viral marker DNA. After ultrasonic treatment of the fast-sedimenting DNA, it shifted to the density positions of viral DNA and, to a lesser extent, that of cellular DNA. The data indicate that the 50-90S viral DNA represents adenovirus DNA covalently integrated into cellular DNA.

106. ADENOVIRUS DNA: TRANSCRIPTION DURING PRODUCTIVE INFECTION, INTEGRATION IN TRANSFORMED CELLS, AND REPLICATION IN VITRO. (PP. 217-236)

Green M, Yamashita T, Buttner W, Fujinaga K, Arens M, Brackmann K, Loni MC
Tumor Virus-Host Cell Interaction. Kolber A, ed. New York, Plenum Press, 1975.

The early and late transcription of the adenovirus 2 genome during productive infection in human KB cells was analyzed by hybridization of RNA in excess with radioactive viral L and H DNA strands. Shortly after infection, transcription of the equivalent of the entire viral DNA genome by cellular enzymes gave two populations of viral RNA: abundant viral RNA transcripts representing 14%-16% of the viral genome; and scarce viral RNA sequences, presumably short-lived precursors to viral RNA. Transcription of the entire viral genome and conservation of specific mRNA molecules apparently present a cellular mechanism for regulating gene expression. The pattern of viral gene transcription changed dramatically when late viral genes began to function. About 80% of viral DNA sequences of the L strand and only 10%-20% of the H strand were transcribed at 9-36 hr. These RNA transcripts were of high abundance and represented the virally imposed regulation of gene transcription. Two major homogeneous early viral mRNA species of mol wt 0.74 and 0.76 x 10⁶ and smaller amounts of 15-18S and 21-26S broad viral RNA peaks were isolated by hybridization with and elution from L and H DNA strands. The number of copies and the fraction of the viral genome in cells transformed by human adenovirus 7 and 12 were estimated by measuring the early reassociation kinetics of denatured viral DNA in the presence of unlabeled transformed

cell DNA. About 300 copies of about 15%-20% of the viral genome were found in adenovirus 7-transformed cells and about 50 copies of about 50% of the genome were found in adenovirus 12-transformed cells. Nuclear membrane fractions containing newly synthesized viral DNA were isolated from adenovirus 2-infected KB cells late after infection. Two polypeptides (of mol wt 75,000 and 45,000) not detected in similar preparations from uninfected KB cells were associated with these fractions. A nuclear membrane complex synthesized short viral DNA fragments *in vitro*.

107. UPTAKE AND FATE OF THE DNA OF ADENOVIRUS TYPE 2 IN KB CELLS.

Groneberg J, Brown DT, Doerfler W
Inst. Genet., Univ. Cologne, West Germany
Virology; 64(1):115-131 1975

The kinetics of uptake and the intracellular fate of human adenovirus DNA were examined in monolayer cultures of KB cells exposed to 3H-labeled adenovirus type 2 DNA. Several procedures were carried out: cell fractionation techniques; acid phosphatase assay; intracellular nucleic extractions; zone velocity sedimentation in neutral and alkaline density gradients; and DNA-DNA hybridization. Cell preparations were variously labeled with 14C sodium formate or 3H-thymidine, and radioactivity was measured by scintillation spectrometry. Infected cells were also examined by electron microscope autoradiography. Studies were carried out in serum-free Eagle's medium under conditions that allowed DNA synthesis to only 18.8% of the level measured in the presence of 10% calf serum. After an initial lag, uptake was linear and reached a plateau at approximately two hours after inoculation, when about 3-9% of the viral DNA were adsorbed. After 2-6 hr, part of the DNA initially adsorbed was shed into the adsorption medium and later partly readsorbed. Viral DNA reached the nucleus beginning at 0.5-2 hr after infection; at 24 hr, 70% of the DNA taken up reached the nucleus. After 24 hr, the amount of label associated with cells exceeded that at any earlier time period. The results were similar when intact type 2 virions were adsorbed to KB cells. Viral DNA was not detected in lysosomes or in cytoplasmic vesicles. Adenovirus-2 DNA was not infectious on HeLa and human embryo kidney cells. Treatment of 3H-DNA with pancreatic DNase abolished the activity, and pretreatment with pronase markedly reduced the infectivity. Incubation of type 2 virus DNA with pronase did not alter the sedimentation profiles of viral DNA in neutral and alkaline sucrose gradients. Endonucleolytic fragmentation of viral DNA occurred in the medium. It is suggested that the parental DNA associated with cellular DNA is integrated into the host genome.

108. A UNIQUE PATTERN OF INTEGRATED VIRAL GENES IN HAMSTER CELLS TRANSFORMED BY HIGHLY ONCOGENIC HUMAN ADENOVIRUS 12.

Green MR, Chinnadurai G, Mackey JK, Green M
St. Louis Univ. Sch. Medicine, St. Louis, MO 63110
Cell (Camb); 7(3):419-428 1976

The viral DNA sequences persisting in HE C19 were analyzed; HE C19 is a clonal line of hamster embryo cells transformed *in vitro* by human adenovirus 12 (Ad 12). Saturation-hybridization of *in vitro*-labeled Ad 12 DNA (2×10^6 to 4×10^6 cpm/ μ g) with HE C19 DNA showed that 93-100% of viral DNA sequences were present in the transformed cell. Reassociation of Ad 12 ³²P-DNA in the presence of HE C19 DNA detected eight viral genome equivalents per diploid quantity of cell DNA. Reannealing each of the six Ad 12 EcoRI restriction DNA fragments with HE C19 DNA indicated that the sequences of each fragment were present in near equimolar quantities, 8-10.5 copies per cell. HE C19 DNA "networks" were prepared and shown to contain the same

viral DNA sequences and in the same amounts as present in unfractionated transformed cell DNA; these data provide the first direct evidence that human adenovirus genes are covalently linked to cellular DNA. The presence of most, if not all, of the viral genes was also demonstrated in the Ad 12 hamster tumor cell line, HT-2. The pattern of integrated viral genes in these nonpermissive hamster cells transformed by Ad 12 is different from that described for cells transformed by group C and B human adenoviruses and simian virus 40.

109. MULTIPLE COPIES OF HUMAN ADENOVIRUS 12 GENOMES ARE INTEGRATED IN VIRUS-INDUCED HAMSTER TUMORS.

Green MR, Mackey JK, Green M
Inst for Molecular Virology, Saint Louis Univ Sch of Med,
St Louis, Mo 63110
J Virol; 22(1):238-242 1977

Tumors induced in hamsters by highly oncogenic human adenovirus 12 contain multiple copies of 90 to 100% of the viral genome in an integrated form. (17 Refs). (Author Abstract)

110. VIRAL GENOME INTEGRATION IN SYRIAN HAMSTER CELLS AFTER CHEMICAL AND VIRUS (MEETING ABSTRACT).

DiPaolo JA, Casto BC, Miyagi M, Popescu NC
Nat'l. Cancer Inst., Bethesda, MD 20014
Proc Am Assoc Cancer Res; 18:94 1977

Enhancement of DNA viral transformation frequency occurs with chemical carcinogens. This enhancement may result from an increased integration of viral genome into cellular DNA. Simian adenovirus (SA7) DNA, associated with singlestrand cell DNA, was determined by cRNA-DNA hybridization following centrifugation in alkaline glycerol gradients and viral DNA in chromosomes by *in situ* hybridization. Four days after 100 μ g/ml MMS or 3 days after treatment with 400 μ g/ml of NiSO₄, there was a 12-fold and a 4-fold increase, respectively, in viral genome content relative to SA7 alone. In the absence of scheduled DNA synthesis, SA7 genome content increased by 4-5 times during the first 24 hrs when virus was added immediately after MMS treatment; no increase occurred when virus was added 24 hrs after MMS. Individually transformed colonies resulting from MMS-SA7 or SA7 alone had similar numbers of SA7 genome/cells. SA7 DNA appears to be inserted randomly among all chromosomes and nuclei and the number of grains varies from cell to cell within a colony. The increased incorporation of SA7 DNA observed shortly after treatment may be due to an increased uptake of viral DNA on a per culture rather than a per cell basis. Alternatively the SA7 DNA may be progressively removed during foci's growth. (Author Abstract)

B. Adenoviruses: Nucleic Acid Hybridization Kinetics

111. AMOUNT OF VIRAL DNA IN THE GENOME OF CELLS TRANSFORMED BY ADENOVIRUS TYPE 2 (LETTER TO EDITOR).

Pettersson U, Sambrook J
Cold Spring Harbor Lab., Cold Spring Harbor, NY 11724
J Mol Biol; 73:125-130 1973

The reassociation kinetics of adenovirus type 2 DNA were measured in the presence of DNAs from control and transformed cells. Reassociation of adenovirus type 2 DNA with DNA extracted from control cells was done at two different concentrations of adenovirus type 2 DNA. The ratios of labeled adenovirus DNA to unlabeled cellular DNA equivalent were 0.79 and 1.58 viral genomes per mammalian genome. The times required for 50% of the viral DNA to reassociate were 24.2 and 48.5 hr, respectively, and were prop-

portional to the concentration of the viral DNA in the soln. The $C_0t_{1/2}$ (the product of the DNA concentration (C_0) and the time (t) taken for 50% of the DNA sequences to reassociate, expressed as moles of nucleotide $\times$ sec/liter) of the reaction was 2.5×10^{-3} mole sec/liter. When 0.79 equivalents of adenovirus 2 DNA were added, the rate of reassociation of the viral DNA was 2.27-fold faster with DNA from transformed cells than with DNA from control cells. The data from the transformed cells indicated that there must have been $(0.79 \times 2.27) = 1.00$ copies of adenovirus 2 DNA per diploid equivalent of cellular DNA. Similar results were obtained with two strains of adenovirus 2 transformed-rat cells. The DNA reassociation curve did not appear to be biphasic thus indicating that the majority of the DNA sequences of the viral genome must be present in the transformed cells.

112. VIRAL DNA SEQUENCES IN CELLS TRANSFORMED BY SIMIAN VIRUS 40, ADENOVIRUS TYPE 2 AND ADENOVIRUS TYPE 5.

Sambrook J, Botchan M, Gallimore P, Ozanne B, Pettersson U, Williams J, Sharp PA
Cold Spring Harbor Lab., Cold Spring Harbor, NY 11724
Cold Spring Harbor Symp Quant Biol; 39:615-632 1974

Cleavage with the restriction endonucleases EcoRI and HpaI followed by hybridization studies were used to measure the quantity of specific fragments of viral DNA in rat cells transformed by adenovirus 2, in hamster cells transformed by adenovirus 5, and in mouse cells transformed by simian virus (SV)40. P32-labeled adenovirus 2 DNA was digested with EcoRI and HpaI and the specific fragments obtained were used to assay for the presence of adenovirus 2 DNA sequences in 10 different lines of transformed rat cells. The renaturation of each specific fragment was measured in the presence of DNA extracted from the transformed cells, calf thymus DNA, and calf thymus DNA to which unlabeled viral DNA had been added. F17 cells contained 3.5 copies, F18 cells, 2.9 copies, F19 cells, 4.9 copies, B1 cells, 6.0 copies and 2T4 cells, 6.9 copies of the viral sequences per diploid quantity of cellular DNA. The four remaining cell lines showed patterns of hybridization which were very different from those displayed by the other six cell lines. The results showed that none of the rat cell lines transformed by adenovirus 2 contained a complete set of viral genes. However, all 10 lines contained the segment of viral DNA that extended from the left-hand end to a point about 14% along the genome. This sequence must code for any viral functions necessary for the maintenance of the transformed state. Two lines of hamster cells transformed by adenovirus 5, HT14a and HT14b, contained 2.4 copies and 5.5 copies of the cleavage fragments per diploid quantity of cellular DNA, respectively. Neither of these transformants contained a complete set of the viral sequences. In mouse cells transformed by SV40 the total wt of the viral DNA was calculated to be approx 4.17 genome equivalents per diploid quantity of cellular DNA. The lengths of the fragments obtained by digestion and their map positions along the viral genomes were also determined. (37 Refs)

113. VIRAL DNA IN TRANSFORMED CELLS. II. A STUDY OF THE SEQUENCES OF ADENOVIRUS 2 DNA IN NINE LINES OF TRANSFORMED RAT CELLS USING SPECIFIC FRAGMENTS OF THE VIRAL GENOME.

Gallimore PH, Sharp PA, Sambrook J
Med. Sch., Birmingham, England
J Mol Biol; 89(1):49-72 1974

In studying the sequences of DNA from adenovirus 2, 32P-labeled adenovirus 2 DNA was treated with restricting endonuclease from Hemophilus parainfluenzae (Hpa I) or restricting endonuclease from Escherichia coli strain RY-13 (EcoRI). The resulting DNA fragments were separated by

means of gel electrophoresis. Measurements were made of the kinetics of renaturation of each of the fragments and also of complete adenovirus 2 DNA. This was done in the presence of DNA, which was extracted from nine lines of rat cells (adenovirus 2-transformed). Of these transformed cell lines, six contained sequences of viral DNA homologous to part of one of the six EcoRI fragments and to two of the seven Hpa I fragments. The cell lines only contain the viral DNA segment stretching from the left end until a point that is 14% along the viral genome. Any viral function that is expressed in the transformed cells has to be coded by this section of the viral DNA.

114. VIRAL DNA IN TRANSFORMED CELLS. I. A STUDY OF THE SEQUENCES OF ADENOVIRUS 2 DNA IN A LINE OF TRANSFORMED RAT CELLS USING SPECIFIC FRAGMENTS OF THE VIRAL GENOME.

Sharp PA, Pettersson U, Sambrook J
Cold Spring Harbor Lab., P. O. Box 100, Cold Spring Harbor, NY 11724
J Mol Biol; 86:709-726 1974

Adenovirus 2 DNA is cleaved into six pieces (A, B, C, D, E, and F) by the restriction endonuclease EcoRI which can be separated by electrophoresis on polyacrylamide-agarose gels. These fragments were used to examine the sequences of viral DNA present in adenovirus 2-transformed rat cells. P32-labeled adenovirus 2 DNA was treated with EcoRI and the resulting fragments were separated by electrophoresis. Kinetics of renaturation of each of the fragments and the complete viral genome were determined in the presence of DNA extracted from transformed rat cells and from control cells. None of the transformed rat cells contained sequences homologous to either fragment B or F. However, all the transformed cells appeared to contain approx 1.65 copies of fragments C, D and E per diploid quantity of cellular DNA. Sequences homologous to fragment A were also observed. The rates of renaturation of P32-labeled fragment A in the presence of transformed cell DNA was smaller than expected for one viral equivalent per diploid quantity of DNA, indicating that each cell must contain sequences homologous to only a fraction of the fragment. When applied to mapping the adenovirus 2 genome, the hybridization data indicated that a contiguous region of the genome was not present in the transformed cells. This missing region consisted of all the sequences of fragments B and F and an unknown portion of those of fragment A and appeared to be from the center of the viral genome. The kinetics of renaturation are discussed. (30 Refs)

115. COVALENT INTEGRATION OF VIRAL DNA INTO CELL DNA IN HAMSTER CELLS TRANSFORMED BY AN AVIAN ADENOVIRUS.

Bellet AJ
John Curtin Sch. Med. Res., Australian Natl. Univ., Canberra
Virology; 65(2):427-435 1975

A method of quantitative analysis for viral DNA integration is described for a kinetic study of integration in nonpermissive, transformable cells. Chick embryo lethal orphan (CELO) virus was grown in chick embryo kidney cells with 1 mCi 32P per culture of 107 cells. The virus was purified and its DNA was extracted. It was fragmented to 400 nucleotides (6.6S). DNA was extracted from hamster skin cells transformed by CELO virus (THS cells) and fragmented to less than 500 nucleotides. 32P-labeled CELO virus DNA fragments (20-80 ng) were mixed with DNA fragments from THS cells or normal hamster cells (BHK), denatured, and allowed to re-associate. The fraction of 32P DNA remaining single-stranded was plotted against time. The slopes obtained

for reassociation of CELO virus DNA in the presence of THS-DNA and BHK-DNA were used to calculate the amount of viral DNA in the sample of THS-DNA. A mean of 15.7 ng of CELO virus DNA per mg of THS cell DNA was obtained and standard error reduced to 3.4 ng. Reassociation of denatured CELO virus DNA in the presence of THS cell DNA showed that transformed cells contain viral DNA. All the viral DNA present in THS cells was integrated into cell DNA by alkali-resistant bonds.

116. REASSOCIATION OF COMPLEMENTARY STRAND-SPECIFIC ADENOVIRUS TYPE 2 DNA WITH VIRAL DNA SEQUENCES OF TRANSFORMED CELLS.

Johansson K, Pettersson M, Philipson L, Tibbetts C
Dept. Microbiology, Biomedical Center, Univ. Uppsala,
Uppsala, Sweden
J Virol; 23(1):29-35 1977

Complementary strand-specific adenovirus DNA, either full length or from restriction enzyme cleavage fragments, was used to estimate the fractional representation and abundance of viral sequences in two adenovirus type 2 (Ad2) transformed rat cell lines, A2F19 and A2T2C4. The reassociation method introduced is based on the linear relationship, after exhaustive hybridization, between the inverted fraction of hybrid DNA and the molar ratio of probe to cellular DNA in the reaction mixture. The amount of viral DNA in A2F19 cells represents 12 to 14% of the viral genome at a level of around seven copies per diploid cell equivalent. For the cell line A2T2C4, the pattern of integrated viral DNA sequences is more complex. With full-length Ad2 DNA strands as a probe, about 56% of the probe was represented in cellular DNA. When each of the four BamHI fragment strands of Ad2 DNA was used as a probe, the fraction of the viral DNA present also amounted to around 56% with one to five copies from different regions of the viral genome. The results demonstrate the advantage of using strand-specific viral DNA as a probe in reassociation analysis with denatured cell DNA. The method should be useful in any system in which complementary strand separation of viral DNA sequence can be achieved. (Author abstract) (22 Refs)

C. Adenoviruses: Dissection of the Integrated Genomes Using Restriction Endonucleases

117. INTEGRATED VIRAL GENOMES IN ADENOVIRUS TYPE 12 TRANSFORMED HAMSTER CELLS.

Groneberg J, Doerfler W
Institut für Genetik der Universität zu Köln, Weyertal 121,
D-5000 Köln 41, West Germany
Hoppe Seylers Z Physiol Chem; 357(3):317 1976

The physical state of the viral DNA in the T637 cell line (adenovirus type 12, AD12-transformed BHK21 cells) was studied by isolating the cellular DNA and cleaving it with various restriction endonucleases. The clearest results were obtained with Sal I endonuclease. A homogeneous peak of fragmented DNA was obtained both by zone velocity centrifugation and electrophoresis and was of higher molecular weight than the largest Sal I fragment of ¹⁴C-labeled AD12 DNA previously added as a marker. The sequences in the peak hybridized with viral DNA on filters up to 30%. DNA from untransformed cells yielded a similar sharp peak after endonuclease digestion, but hybridized less than 5% with the viral DNA. The results are consistent with the model of integrated AD12 genes.

118. INTRACELLULAR FORMS OF ADENOVIRUS DNA: INTEGRATED FORM OF ADENOVIRUS DNA APPEARS EARLY IN PRODUCTIVE INFECTION (MEETING ABSTRACT).

Schick J, Bacsko K, Fanning E, Groneberg J, Burger H, Doerfler W
Inst. Genetics, Univ. Cologne, W. Germany
Proc Natl Acad Sci USA; 73(4):1043-1047 1976

Alkali-stable viral DNAs synthesized in KB cells starting 2-4 hr after productive infection with adenovirus type 2, i.e. before unit length (34S) viral DNA was made. The amount of greater than 100S and 40-100S viral DNA increased when 34S viral DNA synthesis began, and at 16-18 hr postinfection, the 40-100S viral DNA represented 5-20% of the total intracellular viral DNA. The 40-100S viral DNA was synthesized throughout infection. Part of the 40-100S DNA synthesized 5-8 hr postinfection had a density in alkaline CsCl gradients intermediate between those of viral and cellular DNAs. This finding indicates that newly synthesized viral DNA is covalently linked to cellular DNA. Viral sequences were excised from the cellular DNA of infected cells with the EcoRI restriction endonuclease. Fragments of viral DNA were detected in polyacrylamide-agarose gels by DNA-DNA hybridization, and these fragments corresponded in size to most of the known EcoRI fragments of adenovirus 2 DNA. Viral DNA sequences in size-classes between the EcoRI and -C fragments were also found, and probably represent viral DNA linked to cellular sequences.

119. EXCISION OF VIRAL SEQUENCES FROM THE GENOME OF HUMAN CELLS INFECTED WITH ADENOVIRUS TYPE 2.

Bacsko K, Thiessen K, Doerfler W
Institut für Genetik der Universität zu Köln, Weyertal 121,
D-5000 Köln 41, West Germany
Hoppe Seylers Z Physiol Chem; 357(3):306-307 1976

The cellular sequences adjacent to the integrated viral genes were analyzed in human KB cells infected with adenovirus type 2 (Ad2). The cellular DNA was isolated, mixed with an excess of ¹⁴C-labeled Ad2 marker DNA, and cleaved with restriction endonucleases. The fragments were separated and viral sequences were detected by DNA-DNA filter hybridization. On cleavage with EcoRI endonuclease, fragments specific to the virus were produced that corresponded in size to most of the six known Ad2 DNA fragments. The Bam H-I endonuclease cleaved Ad2 DNA into four fragments. Cleavage of cellular DNA from infected cells yielded Ad2 specific sequences, some of which were larger than the largest Bam H-I fragment of the marker DNA. The distribution of Ad2 specific sequences was consistent with the integration of fragments of viral DNA into the eukaryotic chromosome.

120. INTEGRATED VIRAL SEQUENCES IN ADENOVIRUS TYPE 12-TRANSFORMED HAMSTER CELLS.

Groneberg J, Chardonnet Y, Doerfler W
Institute of Genetics, University of Cologne, Cologne,
Germany
Cell (Camb); 10(1):101-111 1977

The physical state of the viral genome in four lines of hamster cells transformed by adenovirus type 12 (Ad12) has been investigated. The four lines of transformed cells originated from hamster cells after infection with Ad12 at multiplicities ranging from 5-350 plaqueforming units per cell. The DNA from transformed cells has been restricted with the Sal I endonuclease from *Streptomyces albus* which cleaves adenovirus DNA more frequently than DNA from adenovirus-transformed hamster cells. Thus after cleavage by

the Sal I enzyme, it is possible to separate free adenovirus DNA sequences from these which are covalently linked to cellular DNA in transformed hamster cells. The results of sequential hybridization experiments in which the Sal I-treated DNA from transformed cells is first annealed to Ad12 DNA on filters, then eluted, and finally hybridized to hamster cell DNA, support the model of Ad12 DNA integrated in multiple fragments into the host genome. Further experiments will be required to characterize the host sequences adjacent to adenovirus DNA and to compare these sequences in different lines of Ad12 transformed cells. (Author Abstract)

D. Adenoviruses: Control of Expression of the Integrated Genome

121. THE MECHANISM OF VIRAL CARCINOGENESIS BY DNA MAMMALIAN VIRUSES: RNA TRANSCRIPTS CONTAINING VIRAL AND HIGHLY REITERATED CELLULAR BASE SEQUENCES IN ADENOVIRUS-TRANSFORMED CELLS (MEETING ABSTRACT).

Tsuei D, Fujinaga K, Green M

Proc Natl Acad Sci USA; 69(2):427-430 1972

Virus-specific RNA was isolated from adenovirus 2-transformed rat embryo cells and from adenovirus 7-induced hamster tumor cells by repeated hybridizations with and elutions from purified homologous viral DNA. Virus-specific 3H-RNA from adenovirus 2-and adenovirus 7-transformed cells hybridized not only with viral DNA (24-40% and 36-50%, resp) but also with DNA purified from untransformed host cells (12-25% and 16-19% resp). 3H-RNA bound insignificantly to empty filters or to filters containing E coli DNA. Virus-specific 3H-RNA derived from KB cells productively infected with adenovirus 2 or 7 hybridized to homologous viral DNA (26-42% efficiency) but not to DNA of untransformed KB, rat, hamster, or E coli cells. It is concluded that RNA molecules containing covalently-linked viral and cellular sequences are transcribed in cells transformed by human adenoviruses and that viral DNA is integrated adjacent to highly reiterated cellular DNA sequences.

122. PRODUCTION OF VIRAL MRNA IN ADENOVIRUS-TRANSFORMED CELLS BY THE POST-TRANSCRIPTIONAL PROCESSING OF HETEROGENEOUS NUCLEAR RNA CONTAINING VIRAL AND CELL SEQUENCES.

Wall R, Weber J, Gage Z, Darnell JE

Dept. Biol. Sci., Columbia U., New York, N. Y.

J Virol; 11(6):953-960 1973

Adenovirus 2-transformed rat embryo cells contain virus-specific sequences which are covalently linked to cell-specific RNA sequences in heterogeneous nuclear RNA (HnRNA) molecules larger than 45S. Virus sequences are identified by hybridization to viral DNA, and the cell sequences are detected by hybridization to cellular DNA under conditions where hybridization occurs only to reiterated sites in cell DNA. Such large composite viral-cell HnRNA molecules presumably arise through the uninterrupted transcription of host sequences and integrated viral DNA. Adenovirus-specific polysomal RNA from these cells sediments as three discrete species at 16, 20, and 26S. These specific classes of viral mRNA do not contain rapidly hybridizing host-specific RNA sequences. Both virus-specific HnRNA and mRNA contain polyadenylic acid sequences since they bind to polyA-terminated HnRNA and mRNA. Thus, the discrete species of virus-specific mRNA in adenovirus 2-transformed cells appear to be derived from high-molecular-wt virus-specific HnRNA through a series of post-transcriptional modifications involving polyA addition. Subsequently the HnRNA is cleaved so that the cell-specific RNA sequences that originate from the reiterated sites in cell DNA do not accompany the adenovirus

mRNA to the cytoplasm. These events for the adenovirus-specific mRNA appear, therefore, to be similar to the stages in the biogenesis of the majority of mRNA in eukaryotic cells.

123. ABSENCE OF ADENOVIRUS-SPECIFIC REPRESSOR IN ADENOVIRUS TUMOUR CELLS.

Weber J

Dept. Microbiol., Cent. Hosp. Univ., Sherbrooke, Canada

J Gen Virol; 22(2):259-264 1974

The possible presence of a repressor-like mechanism responsible for the maintenance of the viral genome in integrated form in the transformed cell was studied using adenovirus type 12 (Ad 12) tumor cells (HTC). Sendai virus mediated fusion of HTC and permissive cells (HEp-2) was used to rescue AD 12 from the former. No evidence of virus rescue was obtained. Heterokaryocytes of HTC and HEp-2 cells were then superinfected with Ad 12 to test for the presence of repressor in the transformed cells. At the highest multiplicity of infection, all of the nuclei of both types of cells generally contained inclusion bodies, the ratio of inclusion bodies in the cells being independent of the relative numbers of the two types of nuclei. Furthermore, both types of heterokaryocytes were represented among the heterokaryocytes. The synthesis of virus antigens by the heterokaryocytes was examined by immunofluorescence. The results indicated that following infection of the heterokaryocyte, the viral proteins were transported to all the nuclei within the heterokaryocyte. The data argue against the presence of a repressor or repressor-like mechanism in the Ad 12 tumor cell.

124. MAPPING OF ADENOVIRUS 2 RNA SEQUENCES IN LYTICALLY INFECTED CELLS AND TRANSFORMED CELL LINES. (PP. 457-474)

Sharp PA, Gallimore PH, Flint SJ

Tumor Viruses Cold Spring Harbor Symposia on

Quantitative Biology. Cold Spring Harbor Laboratory

(Cold Spring Harbor, NY) (39):457-474 1975

In order to map the adenovirus 2 (Ad2) DNA the strands of the six EcoRI fragments and the HpaI fragments E and C of Ad2 DNA were separated. With the use of ³²P-labeled fragment strands in solution hybridization experiments, the fraction of each strand complementary to RNA extracted from infected or transformed cells was assayed. In this manner, a tentative map of the cytoplasmic RNA sequences was constructed for viral RNA extracted from cells both early and late during infection. Since early cytoplasmic RNA annealed to four distinct regions of the genome, Ad2 probably codes for at least four early gene functions. Summation experiments have shown that all RNA sequences found in the cytoplasm of cells early during infection are also present in the cells' cytoplasm at late times. Viral RNA sequences in five independently isolated and cloned transformed rat cell lines were also mapped on the Ad2 genome. One class of Ad2-transformed rat cells, F17, contained RNA sequences complementary to only the segment of Ad2 DNA from 0.03-0.10 on the physical map, and this corresponded to one of the four regions of the genome expressed early during infection. If a viral gene product is necessary to maintain the transformed pheno- type of the cell or codes for the virus-specific tumor (T) antigen, this genetic information must be at the left end of the genome. The two other classes of Ad2-transformed rat cells, 8617 and T2 C4, contained viral RNA sequences complementary to two or three of the regions of the genome transcribed into early cytoplasmic RNA. At both early and late times during the lytic cycle, the nucleus of the infected cell contained viral RNA sequences that were not transported to the cell's cytoplasm, suggesting that RNA processing and selection may play a role in the regulation of viral mRNA production.

125. TRANSCRIPTION OF THE GENOME OF ADENOVIRUS TYPE 12. I. VIRAL MRNA IN ABORTIVELY INFECTED AND TRANSFORMED CELLS.

Ortin J, Doerfler W
Inst. Genetics, Univ. Cologne, West Germany
J Virol; 15(1):27-35 1975

The kinetics of appearance of the polysome-associated adenovirus type 12 messenger (m) RNA in baby hamster kidney (BHK) 21 cells is described. In cells abortively infected with adenovirus type 12, virus-specific RNA was detected 5-7 hr after infection. The amount of RNA reached a maximum between 10 and 12 hr after infection and continued to be synthesized at a reduced level until 48-50 hr postinfection. In BHK-21 cells transformed by adenovirus type 12, 0.26% of the polysome-associated mRNA was virus-specific. The size of the virus-specific mRNA isolated from polysomes of cells abortively infected with, or transformed by, adenovirus type 12 was determined by electrophoresis in polyacrylamide gels in 98% formamide. These conditions eliminated secondary structure or aggregation of RNA. In abortively infected BHK-21 cells viral mRNA size classes of molecular wt 0.9×10^6 and 0.65×10^6 to 0.67×10^6 predominated. A minor fraction of 1.5×10^6 daltons was consistently found and increased with time after infection. Twenty-four to 26 hr postinfection, viral mRNA of 1.9×10^6 daltons was also observed. The size distribution of adenovirus type 12-specific mRNA from transformed cells was similar to that in abortively infected cells, except that the relative amount of the viral mRNA fraction of 1.5×10^6 daltons was much higher. It could not be determined whether the transcripts in abortively infected and transformed BHK-21 cells are derived from integrated viral genomes or from free viral DNA.

126. HYBRIDIZATION OF MRNA FROM ADENOVIRUS-TRANSFORMED CELLS TO SEGMENTS OF THE ADENOVIRUS GENOME.

Bachenheimer S, Darnell JE
Rockefeller Univ., New York, NY 10021
J Virol; 19(1):286-289 1976

Cytoplasmic viral-specific RNA from the 8617 line of adenovirus type 2(Ad2)-transformed rat cells was hybridized to DNA fragments derived by Eco; RI or Sma-I restriction endonucleases. Three viral RNA classes (26S, 20S, and 15S) were detected by hybridization of total cytoplasmic RNA with the RI-A fragment, and all three also hybridized to the much smaller Sma-E fragment of Ad2 DNA. Poly(A)-containing RNA (exposed to 90% formamide) contained only the 20S and 15S mRNA species, suggesting that the 26S RNA might be an aggregated species. Viral RNA of the same size derived from the same regions of the genome was not detected in lytically infected cells, suggesting some change in the transcription pattern or RNA processing of the Ad2 DNA in the integrated state.

127. CONTENT AND EXPRESSION OF INTEGRATED VIRAL DNA IN HAMSTER CELLS TRANSFORMED BY NONDEFECTIVE ADENOVIRUS TYPE 2-SIMIAN VIRUS 40 HYBRID VIRUSES.

Breeden JH, Wewerka-Lutz Y, Schnipper LE, Hauser J, Patch CT, Lewis AM, Levine AS
Section on Infectious Disease, National Cancer Institute, Bethesda, Maryland 20014
J Virol; 20(3):555-563 1976

Hamster cells transformed by adenovirus 2 (Ad2) and five nondefective Ad2-simian virus 40 (SV40) hybrid viruses are all of the Ad2-transformed phenotype. All lines accumulate Ad2 RNA and Ad2 T antigen; two hybrid-transformed lines accumulate SV40 RNA, but only one contains detectable amounts of SV40 antigens. We examined selected lines from this

group of transformed hamster cells for Ad2 DNA content and viral RNA expression by using hydroxyapatite chromatography and separated strands of labeled viral DNA as probes. All lines studied contain 1 to 2 Ad2 genome equivalents per haploid equivalent of cell DNA. The expression of Ad2 RNA exhibits two distinct patterns. In one pattern, transcription of the heavy strand of Ad2 DNA is less extensive than that of the light strand, whereas in the second pattern of Ad2 RNA expression the extent of heavy-strand transcription is greatly increased. In the two lines containing SV40 RNA, the entire SV40 (-) strand is transcribed; the (+) strand is not expressed in these cells. These patterns of viral RNA expression suggest the possibility that host promoters may play a role in regulating transcription of integrated viral DNA. (Author Abstract)

E. Adenoviruses: Control of Integration

128. EARLY EVENTS IN ADENOVIRUS-INFECTED CELLS. (PP. 551-557)

Russell WC
Tumor Viruses Cold Spring Harbor Symposia on Quantitative Biology. vol. 39, Cold Spring Harbor Lab. (Cold Spring Harbor, NY, 1975).

Serological, polypeptide synthesis, and temperature-sensitive mutant studies on adenovirus-infected cells are reviewed. Serological studies suggest that adenovirus-derived tumors have components that are related to both nonstructural and structural (possibly fiber) antigens. Recent evidence suggests that core proteins are synthesized early in infection, and since the synthesis of cellular histones is inhibited later in infection, it is suggested that the basic core polypeptides may play a role in the replication of virus DNA somewhat analogous to that of histones. If infected cell-specific polypeptides and the core polypeptides are associated with the replication of viral DNA, they may be DNA-binding proteins. The early findings that broad tumor sera react type-specifically with fiber antigen can be explained by the possibility that some of the reactions against structural components can be related to antibody against the core components (probably made early in infection), or the possibility that the fiber antigen preparations were not rigorously purified. These studies indicate that only a few possible viral gene products can be detected early in a lytic infection or in an abortive infection. Some or all of these products appear to be concerned with initiating and maintaining viral DNA synthesis; failure to do so may lead to integration of the viral genome into the cellular chromosome. The integrated viral genome would probably express a viral gene function that would kill the host; in a few cases, the functions that are integrated or expressed may be compatible with the coexisting cellular functions and thus could lead to transformation and oncogenesis.

129. CELL TRANSFORMATION: A STUDY OF REGULATION WITH TYPES 5 AND 12 ADENOVIRUS TEMPERATURE-SENSITIVE MUTANTS. (PP. 419-426)

Ginsberg HS, Ensinger MJ, Kauffman RS, Mayer AJ, Lundholm U
Tumor Viruses Cold Spring Harbor Symposia on Quantitative Biology. vol. 39, Cold Spring Harbor Lab. (Cold Spring Harbor, NY, 1975).

The types 5 and 12 temperature sensitive (ts) mutants of adenovirus (Ad) that cannot replicate their DNA under nonpermissive conditions (39.5 C) are described. In addition, one that can make the major viral gene products but under nonpermissive conditions cannot transport its hexon protein into the nucleus for virion assembly is characterized. The following insights were achieved: (a) viral DNA replication requires at least two specific viral proteins; (b) hexon protein

transport requires a nonhexon viral protein; (c) virions assembly cannot ensue if one of the viral gene products is defective; and (d) transformation is the consequence of abortive infections with many adenoviruses, but its incidence is increased after infection with one class of adenovirus ts mutants. Two models are presented to explain the last observation. In one model, the DNA-binding protein normally maintains the viral DNA in a specific conformation or attached to some cellular structure so that viral genome integration is prohibited and viral DNA replication is initiated and continues. In the absence of this protein integration is more commonly permitted. In the second model, viral genome integration into a host chromosome is a normal event in the initial stages of infection, even during a productive infection. The latter hypothesis suggests that in a normal productive infection the entire viral genome is excised and replicated; defective excision occurs in abortively infected cells, leaving genome fragments to initiate and maintain transformation.

130. SIGNIFICANCE OF TREATMENT INTERVAL AND DNA REPAIR IN THE ENHANCEMENT OF VIRAL TRANSFORMATION BY CHEMICAL CARCINOGENS AND MUTAGENS.

Casto BC, Pieczynski WJ, Janosko N, DiPaolo JA
BioLabs, Inc., 2910 MacArthur Blvd., Northbrook, IL
60062

Chem Biol Interact; 13(2):105-125 1976

Treatment of Syrian hamster embryo cells with diverse classes of chemical carcinogens enhanced transformation by a carcinogenic simian adenovirus, SA7. Optimal enhancement was a function of time of chemical addition in relation to time of virus addition and cell transfer. Aflatoxin B1 and the polycyclic hydrocarbons, benzo(a)pyrene, 3-methylcholanthrene, and 7,12-dimethylbenz(a)anthracene enhanced SA7 transformation when added prior to virus, but inhibited transformation when added after virus adsorption and cell transfer. The enhancement of SA7 transformation was maximal when cytosine arabinoside, caffeine and 6-acetoxy-benzo(a)pyrene were added after virus, but minimal when these were added before virus. A third class of chemicals, including b-propiolactone, methyl methanesulfonate, N-acetoxy-2-acetylaminofluorene, N-methyl-N9-nitro-N-nitrosoguanidine, and methylazoxymethanol acetate, enhanced SA7 transformation when added before, or after, virus inoculation and cell transfer. All chemicals, which induced changes in DNA sedimentation in alkaline sucrose gradients and unscheduled DNA (repair) synthesis, increased the frequency of SA7 transformation. However, several chemicals such as dibenz(a,h)anthracene, benzo(e)pyrene, cytosine arabinoside, and caffeine enhanced SA7 transformation but did not induce DNA sedimentation changes or repair. Chemicals that cause reparable DNA damage may provide additional sites for integration of viral DNA during the repair process, but those that do not induce DNA repair synthesis may enhance viral transformation by incorporation of viral DNA into sites of unrepaired cell DNA during regular DNA synthesis.

131. LESS TUMORIGENIC (CYT) MUTANTS OF ADENOVIRUS 12 DEFECTIVE IN INDUCTION OF CELL SURFACE CHANGE.

Yamamoto H, Shimojo H, Hamada C
Dept. Enteroviruses, Natl. Inst. Health,
Musashimurayama, Tokyo 190-12, Japan
Virology; 50:743-752 1972

Less tumorigenic mutants of adenovirus 12 were isolated and compared with the wild type (w) to identify the viral function necessary for tumorigenesis. Two less tumorigenic (lt) clones, lt3 and lt5, were isolated from human embryo kidney (HEK) cell cultures. Comparative studies of lt3 and lt5 with w

revealed no differences in various properties of virion structure, such as antigenicity, polypeptide composition and heat stability. Growth in HEK cells did not differ between the mutants and w. However, in lt3-infected cultures, the virus titer in the medium at 48 hr postinfection was higher than in w-infected cultures. This suggested that lt3 virions were liberated from cells into medium more efficiently than w virions. In HEK cells, the mutants formed large, clear plaques, whereas w formed fuzzy-edged plaques. The mutants and w did not differ in their cell-killing capacity, their capacity to induce cellular DNA synthesis, or in the integration of viral DNA into cellular DNA. The mutants were found to be ineffective in inducing transplantation immunity. The agglutination of cells by lectin demonstrated that the concentrations of lectin necessary to agglutinate uninfected cells and mutant-infected cells were not significantly different, but cells infected with w agglutinated in the presence of lower concentrations of lectin. The results suggest that the lt mutants are defective in inducing cell surface change but not for replication. These observations indicate that cell surface change might be necessary for cell transformation. (25 Refs)

F. Adenoviruses: Use of Infectious DNA-Transfection

132. TRANSFORMATION OF RAT CELLS BY DNA OF HUMAN ADENOVIRUS 5.

Graham FL, Van Der Eb AJ
Lab. Physiological Chem., State U. Leiden, The
Netherlands
Virology; 54(2):536-539 1973

Primary rat embryo and baby rat kidney cells were transformed by human adenovirus 5 DNA (Ad 5 DNA). Approximately two to three wk after exposure of rat embryo cells to Ad 5 DNA, foci of small, densely packed, round or cuboidal cells were observed over a background of normal fibroblasts. In baby rat kidney cultures, however, foci could often be observed within as little as 10 to 12 days after exposure to DNA, and after 3 wk many colonies were as large as 2-3 mm. As in the case of the rat embryo cells, these foci contained small, round, densely packed cells characteristic of adenovirus transformation. From morphological and immunological evidence it could be shown that the transformation in DNA treated cultures was adenovirus specific. Transforming activity was resistant to heating (1 hr at 56 C), and to pronase, but was sensitive to DNase. The efficiency of transformation was approximately 1 transformed focus/microg DNA.

133. STUDIES ON IN VITRO TRANSFORMATION BY DNA AND DNA FRAGMENTS OF HUMAN ADENOVIRUSES AND SIMIAN VIRUS 40. (PP. 637-650)

Graham FL, Abrahams PJ, Mulder C, Heijneker HL,
Warnaar SO, De-Vries FA, Fiers W, Van-Der-Eb AJ
Tumor Viruses Cold Spring Harbor Symposia on
Quantitative Biology. vol. 39, Cold Spring Harbor Lab.
(Cold Spring Harbor, NY, 1975).

Attempts were made to locate and isolate segments of adenovirus and SV40 DNA that are able to transform cells in vitro. DNA fragments were prepared by mechanical shear or by incubation with restriction endonucleases; single-stranded ends were generated by exonuclease III digestion. Transformation assays were made with primary rat kidney cell cultures using the calcium assay technique. Noninfectious, mechanically broken DNA fragments retained their transforming capacity, even fragments as small as 3×10^6 daltons or one-eighth of the adenovirus 5 genome. DNA fragments sedimenting slower than approximately 10S had no transforming activity. The length of the transforming segment was not greater than about 1×10^6 daltons, or 4%-5% of the

adenovirus 5 genome. The transforming segment begins at 1.1% from the left terminus of the molecule and terminates at about 5%-6%, about 350 base pairs from the terminus. A specific fragment with transforming activity could be isolated from adenovirus 2 and 5 DNA digested with endonuclease R;HsuI. This fragment had a molecular weight of 1.6×10^6 daltons and represented the left terminal fragment of both DNA's. Primary hamster kidney cells (which are permissive for adenovirus 5) were readily transformed by shear-induced fragments of adenovirus 5 DNA; human embryonic kidney cells were much less readily transformed. Hamster cells transformed by adenovirus 5 DNA produced tumors in newborn hamsters, while similarly transformed rat kidney cells produced tumors in newborn isologous rats. The transformed cell lines were positive for adenovirus T antigen. With the calcium technique, SV40 DNA transformed both primary rat kidney cells and mouse 3T3 cells. The rat cells were also transformed with linear molecules of SV40 DNA and with SV40 DNA fragments.

134. SIZE AND LOCATION OF THE TRANSFORMING REGION IN HUMAN ADENOVIRUS TYPE 5 DNA.

Graham FL, Van der Eb AJ, Heijneker HL
Dept. Biology, McMaster Univ., Hamilton, Ontario L8S 4L8, Canada
Nature; 251:687-691 1974

Studies were undertaken to prove that adenovirus type 5 (Ad 5) DNA fragments of less than genome size have transforming activity, to determine the minimum size of fragments which retain transforming activity, and to map the location of the transforming (T) segment within the viral DNA molecule. Fragmentation experiments showed that the transforming activity began to decrease when the DNA fragment size fell below about 2×10^6 daltons and was completely abolished at fragment sizes below 1×10^6 daltons. Cells transformed by small DNA fragments did not appear to differ morphologically from those transformed by intact DNA. Enzyme cleavage experiments revealed that the T segment was located on the guanosine-cytosine-rich half of the Ad 5 DNA molecule and that it begins at 1% from the left end of the Ad 5 genome and terminates at about 5-6%. (25 Refs)

IV. INTEGRATION OF HERPESVIRUS WITH THE CELLULAR CHROMOSOME

A. Herpes Simplex Virus Integration

135. PRESENCE OF A HERPES SIMPLEX VIRUS DNA FRAGMENT IN AN L CELL CLONE OBTAINED AFTER INFECTION WITH IRRADIATED HERPES SIMPLEX VIRUS 1.

Kraiselburd E, Gage LP, Weissbach A
Roche Inst. Molecular Biology, Nutley, N. J. 07110
J Mol Biol; 97(4):533-542 1975

Herpes simplex virus DNA sequences were detected in a mouse cell line selected for thymidine kinase activity after infection of a parental L cell thymidine kinaseless strain with irradiated Herpes simplex virus type 1. One of these clones (no. 139) was analyzed for the presence of the virus genome. Reassociation kinetic analyses using iodinated virus DNA (60 hr at 75°C) established that there were five copies of a fragment comprising about 23% of the virus genome in each clone cell. This value could be an underestimate because reactions of sufficient duration and Herpes simplex virus DNA concentration to reassociate all the Herpes simplex virus probe DNA were not performed. Neither the parental thymidine kinaseless L cell line nor a revertant cell line obtained from the clone showed any detectable virus DNA-specific sequences. These results suggest that the thymidine kinase activity is

probably encoded by a fragment of the viral genome integrated in the DNA of the clone 139 cells.

136. ASSOCIATION OF HERPES SIMPLEX VIRUS TYPE 1 DNA WITH HOST CHROMOSOMAL DNA DURING PRODUCTIVE INFECTION.

Biegeleisen K, Rush MG
New York Univ. Sch. Medicine, 550 First Ave., New York, NY 10016
Virology; 69(1):246-257 1976

Reassociation kinetics were used to study herpes simplex virus type 1 (HSV-1) DNA in the total DNA isolated from productively infected African green monkey kidney (BSC-1) cells. Cesium chloride equilibrium density gradient centrifugation of total DNA from infected cells gave distinct peaks of viral and host cell nucleic acids. Reassociation kinetics revealed viral sequences in the host peak. Host cell DNA further purified by repeated CsCl density gradient centrifugations also contained viral sequences. Contamination of this purified material with viral DNA accounted for very few of these sequences, and buoyant-density heterogeneity of fragmented HSV-1 DNA is integrated into host chromosomal DNA during productive infection. A repetitive sequence of productive and lysogenic interactions could result in latent-recurrent herpes infections.

137. FURTHER STUDIES ON THE ASSOCIATION OF HERPES SIMPLEX VIRUS TYPE 1 DNA WITH HOST DNA DURING PRODUCTIVE INFECTION.

Biegeleisen K, Yanagi K, Rush MG
Dept. Biochemistry, New York Univ. Sch. Medicine, 550 First Ave., New York, NY 10016
Virology; 83:221-225 1977

The effects of the time course, temperature, and multiplicity of infection on the association between herpes simplex virus type 1 (HSV-1) and African green monkey kidney (BSC-1) DNAs in productively infected cells were studied. The interaction of host and viral DNAs was found to be dependent on both the concentration of intracellular viral DNA and on the particular conditions of infection. Examination of the time course of infection demonstrated that the amount of free viral DNA per cell reached a max much earlier than the viral-host-associated DNA. The amount of free viral DNA remained essentially constant over the temperature range of 33.5-39.5°C, whereas the viral-host-associated DNA showed a three-fold variation over this range. Depending on the conditions of infection, the quantity of HSV-1 DNA associated with host cell DNA ranged from 100 to 1,500 genome equivalents per cell. Only 5 to 40% of this association was alkali stable. (19 Refs)

B. Epstein-Barr Virus Integration

138. FATE OF VIRUS DNA IN THE ABORTIVE INFECTION OF HUMAN LYMPHOID CELL LINES BY EPSTEIN-BARR VIRUS.

Jehn U, Lindahl T, Klein G
Karolinska Inst., Stockholm, Sweden
J Gen Virol; 16(3):409-412 1972

The fate of 3H-prelabeled Epstein-Barr (EB) virus DNA was investigated after abortive superinfection of two different human lymphoid cell lines (Raji and NC37). At 40 hr after infection when "early antigen" was being expressed, the cells were lysed and the cellular distribution of radioactivity was determined. Approximately 50% of the total intracellular radioactivity was found in the nuclei. More than 50% of this 3H-labeled nuclear DNA was present in a DNase-sensitive form. Sucrose density and CsCl equilibrium density centrifugation studies showed that the labeled intranuclear

DNA was undegraded, non-integrated EB virus DNA. These results therefore did not support the concept of covalent association between virus DNA and cellular DNA, and integration of virus DNA on a scale observed in other systems. It was also concluded that the observed expression of early virus functions 20 to 50 hr after superinfection of lymphoid cells may depend on transcription of the incoming EB virus DNA.

139. LINEAR ASSOCIATION BETWEEN CELLULAR DNA AND EPSTEIN-BARR VIRUS DNA IN A HUMAN LYMPHOBLASTOID CELL LINE (MEETING ABSTRACT).

Adams A, Lindahl T, Klein G

Depts. Tumor Biol. Chem., Karolinska Inst., Stockholm, Sweden

Proc Natl Acad Sci USA; 70(10):2888-2892 1973

High-molecular-wt DNA from cell line Raji (derived from Burkitt's lymphoma), which contains 50-60 copies of Epstein-Barr virus DNA per cell, was fractionated in neutral solution by several cycles of CsCl gradient centrifugation in fixed-angle rotors. Under the fractionation conditions used, intact Epstein-Barr virus DNA from virus particles can be separated from the less-dense cellular DNA. In contrast, a large proportion of the intrinsic Epstein-Barr virus DNA component of Raji cells remains associated with cellular DNA, as determined by nucleic acid hybridization. This interaction, which is resistant to Pronase and phenol treatment, is not the result of aggregation. When the molecular weight of Raji DNA is reduced by hydrodynamic shear, the amount of virus DNA associated with cell DNA decreases. However, some virus DNA still remains bound to fragments of cellular DNA after shearing. The association is completely destroyed in alkaline solution. Molecular wt analysis of Raji DNA after denaturation showed that the alkali-induced release of Epstein-Barr virus DNA was specific and not the result of random single-strand breaks. These data indicate that Epstein-Barr virus DNA is linearly integrated into Raji cell DNA by alkali-labile bonds.

140. LATENT DNA OF EPSTEIN-BARR VIRUS: SEPARATION FROM HIGH-MOLECULAR-WEIGHT CELL DNA IN A NEUTRAL GLYCEROL GRADIENT.

Tanaka A, Nonoyama M

Dept. Microbiology, Rush-Presbyterian-Saint Luke's Medical Center, Chicago, IL 60612

Proc Natl Acad Sci USA; 71(12):4658-4661 1974

The separation of latent Epstein-Barr virus (EBV) DNA from high mol wt cell DNA in a neutral glycerol gradient is described. Raji cells, an established cell line from a patient with Burkitt's lymphoma, were lysed with sarkosyl alone or with sarkosyl and pronase, and a mixture of Simpson cells and purified EBV treated with sarkosyl and pronase were evaluated by neutral glycerol velocity centrifugation. Treatment of Raji cells with sarkosyl alone did not separate the major portion of EBV DNA from cells EBV DNA (C) from cell DNA. There was, however, a small amount of EBV DNA (C) detectable in the 55Svedberg (S) region. Treatment of the Raji cells with both sarkosyl and pronase enhanced the separation of EBV DNA (C) from cell DNA and about 70-80% of the EBV DNA (C) was recovered as 55S DNA. Similar results were obtained with the mixture of Simpson cells and EBV treated with sarkosyl and pronase. The CsCl density of the EBV DNA (C) from the Raji cells was 1.713-1.714 g/cm³. This indicated that the 55S EBV DNA (C) might be linked to pieces of cellular DNA or that some proteins might be bound to the 55S EBV DNA (C). Further centrifugation in CsCl in the presence of sarkosyl shifted the density to 1.716-1.717 g/cm³, which was very close to the density of EBV DNA from the virus. The results demonstrated that the majority of EBV

DNA (C) in Raji cells was not linearly associated with high mol wt cell DNA. (10 Refs)

141. INTEGRATION OF EPSTEIN-BARR VIRUS DNA INTO CELLULAR DNA OF BURKITT LYMPHOBLASTS (RAJI CELL LINE).

Becker Y, Shilomai J, Weinberg E, Ben-Zeev A, Olshevsky U

Hebrew U.-Hadassah Med. Sch., Jerusalem, Israel
Isr J Med Sci; 10(1):1454-1457 1974

Purified Raji cell DNA was banded in neutral CsCl gradients and the DNA of each fraction was melted and hybridized with Epstein-Barr virus (EBV)-32P-cRNA. Cellular DNA banded at a mean density of 1.700 g/ml (range 1.680-1.710 g/ml). Two peaks of 32P-cRNA-DNA hybrids were detected; one peak at a density of 1.707 g/ml and the other at a density of 1.700 g/ml. Thus, the EBV-DNA sequences are tightly bound to cellular DNA molecules which have a density much lower than that of EBV-DNA (1.718 g/ml). Shearing of Raji DNA molecules resulted in the appearance of EBV-DNA sequences which banded at a density of 1.710 g/ml. Alkali denaturation of Raji cell DNA also showed that most of the EBV-DNA molecules banded at a density lower than that of free EBV-DNA. Only a small fraction of the viral DNA molecules banded at the density of denatured free EBV-DNA, most fragments remaining associated with cellular DNA.

142. LATENT GENOMES OF EPSTEIN-BARR VIRUS. (PP. 133-137)

Tanaka A, Nonoyama M

Oncogenesis and Herpesvirus II Part 1: Biochemistry of Viral Replication and in Vitro Transformation
Proceedings of a Symposium held in Nuremberg, Federal Republic of Germany, 14-16 October 1974. International Agency for Research on Cancer. (Lyon, France, 1975.

Of the Epstein-Barr virus DNA's in Raji cells that contained 50 to 60 viral genomes per cell, 90% were separated from high molecular weight cellular DNA by centrifugation. It was performed in a neutral glycerol gradient after the cells were lysed by treatment with pronase and Sarkosyl, indicating that the major portion of the EBV DNA in Raji cells was not integrated linearly into cellular DNA.

143. EPSTEIN-BARR VIRUS GENOMES WITH PROPERTIES OF CIRCULAR DNA MOLECULES IN CARRIER CELLS (MEETING ABSTRACT).

Adams A, Lindahl T

Karolinska Inst., Stockholm, Sweden

Proc Natl Acad Sci USA; 72(4):1477-1481 1975

The DNA conformation of Epstein-Barr Virus (EBV) genomes in Raji cells is reported. Raji cells were grown in suspension cultures in RPMI 1640 medium with 10% fetal bovine serum. DNA was prepared by cell lysing using 3% Sarkosyl and 1% pronase, and was precipitated with CsCl. Raji 3HDNA in CsCl was supplemented with 10 ng/ml of sheared Klebsiella pneumoniae 14CDNA as reference marker and centrifuged for 65 hr at 33,000 rpm, 20 C. Fractions were collected and removed for determinations of 3H and 14C radioactivity, and for the ability to hybridize with 32PRNA complementary to EBV DNA. Fractions were further analyzed on neutral glycerol gradients (with phage T4 14CDNA added as reference), and on CsCl/propidium diiodide gradients. EBV DNA sedimented more slowly than T4 DNA at 0.94-0.95 times the rate of phage DNA. Approximately 80% of the total EBV DNA applied to the CsCl gradient was recovered in the high density region with a peak at 1.716 g/cm³. Free viral DNA sedimented at 1.718 g/cm³. Using neutral glycerol gradients the majority of EBV DNA sedimented into two distinct peaks, 65S and 100S. When Raji 3HDNA from the 95-

110S regions were analyzed, 8-10% of the total DNA banded as a small peak at the position of the covalently closed circular DNA. The remaining DNA banded as linear or nicked circular DNA. The small peak contained 50% of the total EBV DNA recovered. Using the CsCl/propidium gradient, 95% of the EBV DNA sequences present banded together with the cellular DNA. It appears that latent EBV DNA has the properties of a mammalian episome. Both nonintegrated and integrated viral DNA sequences can be isolated from carrier cells.

144. REPLICATION AND LATENCY OF EPSTEIN-BARR VIRUS.

Nonoyama M, Tanaka A, Yajima Y

Dept. Microbiology, Rush-Presbyterian St. Luke's Medical Center, 1753 West Congress Parkway, Chicago, IL 60612
Bibl Haematol ; (43):291-296 1976

Raji cells were superinfected with Epstein-Barr virus (EBV) to determine the extent of viral infection and the cause of viral replication blockage in superinfected cells. The virus recovered from superinfected Raji cells was noninfectious in a second cycle of infection. Nonproductive Raji cells transformed by EBV have nonintegrated plasmid type DNA as the majority of the viral genomes. Small amounts of EBV DNA could be integrated into cellular DNA in transformed cells. The function of EBV genomes in transformed cells is not fully understood. Treatment of HRI-virus producing cells with cycloheximide converted the cells to nonproductive cells and reduced the number of EBV genomes per cell from 350 to 10. One cell line, No. 9, was isolated that carried only a single EBV genome per cell. It was shown that some EBV DNA could be separated from high molecular weight cellular DNA. The data are not conclusive, but they suggest that the single EBV genome in No. 9 cells may not be integrated into cellular DNA in an alkaline stable form. Hybridization kinetics suggested two possibilities: (1) transcription of EBV genomes in transformed cells is restricted, and transcription of not more than a few percent of EBV genomes may be required in transformed cells, or (2) 20% of the region of each EBV DNA may be transcribed only several times in one cycle. In relation to the latter, the viral genome may be transcribed only at the early S phase, the time when all EBV DNA in Raji cells duplicates. (8 refs)

145. COVALENTLY CLOSED CIRCULAR DUPLEX DNA OF EPSTEIN-BARR VIRUS IN A HUMAN LYMPHOID CELL LINE.

Lindahl T, Adams A, Bjursell G, Bornkamm GW, Daschka-Dierich C, Jehn U

Dept. Chemistry, Tumor Biology and Biochemistry, Karolinska Inst., 104 01 Stockholm, Sweden
J Mol Biol; 102(3):511-530 1976

A nonintegrating form of Epstein-Barr virus (EBV) DNA was purified from the Burkitt lymphoma-derived human lymphoid cell line Raji by CsCl density gradient centrifugation and neutral glycerol gradient centrifugation. This intracellular form of the virus DNA sedimented at a rate typical of a covalently closed circular DNA molecule of the size of the virus genome in both neutral and alkaline solution. X-irradiation (500 rads) led to a form with the sedimentation properties of open circular DNA (a circular duplex molecule containing one or more single-strand breaks). The direct observation of large circular DNA molecules by electron microscopy confirms the covalently closed circular duplex structure of part of the intracellular viral DNA. Such circular molecules were not detected in corresponding DNA fractions from EBV-negative human lymphoid cell lines. In ethidium bromide/CsCl density gradient centrifugation experiments, the purified nonintegrated virus DNA behaved as twisted, covalently closed DNA circles with two same initial superhelix

density as polyoma virus DNA. With the latter technique intracellular EBV DNA was isolated in greater than 90% form from nonproducer cells. The molecular weight of the circular virus DNA from Raji cells, determined by contour length measurements, is the same (within experimental error) as that of the linear DNA from virus particles.

146. CIRCULAR EPSTEIN-BARR VIRUS GENOMES OF REDUCED SIZE IN A HUMAN LYMPHOID CELL LINE OF INFECTIOUS MONONUCLEOSIS ORIGIN.

Adams A, Bjursell G, Kaschka-Dierich C, Lindahl T
Departments of Tumor Biology, Biochemistry, and Chemistry, Karolinska Institute, 104 01 Stockholm, Sweden

J Virol; 22(2):373-380 1977

Circular Epstein-Barr virus (EBV) DNA molecules have been purified and characterized from a human lymphoid cell line derived from a case of heterophile antibody-positive, blood transfusion-induced infectious mononucleosis, 883L. The circular EBV DNA in three cell lines obtained by transformation of human umbilical cord blood leukocytes with a strain of EBV originally derived from 883L was also studied. As estimated from sedimentation velocity data and electron microscopy, the circular EBV DNA molecules are 10 to 15% smaller than either the circular EBV DNA previously found intracellularly in several other types of EBV-transformed cells or the linear EBV DNA present extracellularly in virus particles. In addition, the EBV-transformed cord blood cell lines studied here differed from other EBV-transformed cells in that integrated virus DNA sequences could not be detected. (39 Refs) (Author Abstract)

V. REVIEW ARTICLES ON ONCOGENIC VIRUSES AND INTEGRATION

A. General Overviews on Oncogenic Viruses and Their Integrated Genomes

147. BENEFITS OF INTEGRATION.

Lewin R

No affiliation

New Sci; 60(87):401-403 1973

Vertical transmission of viral genetic material (passage from parent to offspring) can be achieved in a number of ways, including genetic transmission (intimate association of the virus with the genetic material of the germ cells). Many viruses achieve this intimacy by physically integrating their genomes into the hosts', seemingly preferably in the protein coding regions of host DNA chains. The enzyme reverse transcriptase, or RNA-direct DNA polymerase, is used by the RNA virus to produce a DNA copy of itself (provirus) prior to integrating with the host. The virus then appears to slip into and out of the host's genes quite frequently, often removing a piece of the host cell's DNA or leaving a piece of its own DNA as it is excised. It appears that a similar process may occur within normal cells. Reverse transcriptase, which has been discovered in a number of embryonic tissues, may play a role in cell differentiation. According to this theory, (provirus theory) the information coded for in genes might be shifted around within and between cells via RNA intermediates, thus exploiting the variability inherent in the genetic information. However, since this process is not always precise, wholly new DNA sequences could be created within the lifetime of a single organism simply from the mistakes of the provirus system. Some of the mistakes could produce new DNA inimical to the cell; thus the DNA sequences necessary for cancer formation might easily be assembled, as might an RNA virus.

148. VIRUSES AS THE POSSIBLE CAUSE OF CANCER.

Van der Noordaa J

Lab. Gezond., Amsterdam, Netherlands

Maandschr Kindergeneeskd; 42(9-10):365-368 1974

Evidence for a possible viral etiology of some human tumors is reviewed. There is considerable evidence that viruses are responsible for the development of leukemia and sarcomas in mice and chickens. However, the human equivalent of these oncornaviruses has not yet been found, despite many attempts. Although there is some evidence for the presence of murine oncornavirus genetic material in human leukemic cells, these findings are difficult to interpret. Similarly, although an oncornavirus has been isolated from the mammary tumors of mice, no such virus has been found in humans. In contrast, the herpes viruses have been related to the pathology of Burkitt's lymphoma and cervical carcinoma in humans; herpes viruses have also been isolated and found to cause Marek's disease, renal carcinoma, and some lymphomas in various animal species. Another group of viruses, the human adenoviruses, can induce tumors in hamsters but seem unable to do so in the natural host. Among the papovaviruses, the Simian virus 40 (SV40) has been used to study the mechanism of cell transformation. These studies have shown that the viral genetic material remains in the transformed cell and that the viral DNA becomes integrated into the cellular DNA. Integration of the viral DNA may be an important step in both normal viral multiplication and the transformation process as a whole. Integration and subsequent excision of the viral DNA from cellular DNA seems to occur during viral multiplication; the significance of this finding is unclear.

149. CHROMOSOME INTEGRATION OF VIRAL DNA: THE OPEN-REPLICON HYPOTHESIS OF CARCINOGENESIS. (PP. 41-76)

Whitehouse HL

Chromosomes and Cancer. German J, ed. New York, John Wiley and Sons, 1974.

Evidence concerning the existence of viruses in a proviral state (integrated into the host DNA), the association between integrated animal viruses such as polyoma virus and simian virus 40 and cancer, and the carcinogenic mechanisms of ionizing radiations, many chemicals, and certain genetic defects in relation to viral carcinogenesis is reviewed. Evidence for the open-replicon hypothesis of carcinogenesis is presented. This hypothesis assumes that integration of a viral genome into a host chromosome has selective advantages for both virus and host (immunity to the virus for the host and survival for the virus), that viral carcinogenesis is a consequence of the triggering of host DNA synthesis (necessary for integration of viral genomes), with the breakdown of replication control that this entails, and that physical and chemical carcinogens inactivate (by mutation) host genes whose products normally check the proviral genes that can initiate host DNA synthesis. Genetic defects associated with a high cancer risk may affect the immunologic responses of the host, or they may alter the balance between proviral genes and their suppressors, either directly or through mutation. It is concluded that the data on carcinogenesis by physical and chemical agents, or in association with genetic defects, seem to be in agreement with the hypothesis that cancer induction is primarily the result of inactivation of suppressor loci that normally block the action of transformation-inducing proviral genes. A similar hypothesis may also explain differentiation. (137 refs)

150. KNOWLEDGE AND IGNORANCE ABOUT THE MOLECULAR BIOLOGY OF SMALL ONCOGENIC DNA CONTAINING VIRUSES. (PP. 3-11)

Dulbecco R

Tumor Virus-Host Cell Interaction. Kolber A, ed. New York, Plenum Press, 1975.

The molecular biology of polyoma virus and simian virus 40 (SV40) is discussed. The degree of permissiveness and how it affects expression of the viral genome accounts for the various types of stably transformed cultures. Two main conditions probably determine permissiveness: (a) how frequently the provirus is detached from the host chromosome, and (b) how efficiently the detached genome can be expressed. It is postulated that the T, U, and TSTA antigens are different determinants of the same molecule or cellular molecules modified by the virus. The mechanism of DNA aberrations is not yet clear. Oligomers of complete as well as of defective molecules could be produced either by an accident of replication or by homologous recombination. The DNA aberrations suggest that recombination of viral DNA occurs by the mechanisms recognized in cellular DNA. Unresolved aspects of integration include the sites on the cellular chromosomes (receptor sites), the sites on the viral chromosome that participate in integration (donor sites), and the enzymes involved. Other questions are whether integration has other roles besides anchoring viral DNA to cellular DNA and whether it is required for stable transformation in all systems. A general question concerning both excision and integration is whether they are carried out through a single act of recombination between specific sites. A single act seems likely, because viral DNA is cyclic and native linear intermediates are unknown. There is no direct evidence on whether there are specific viral sites for insertion and excision. A reasonable position concerning transcription is that physiological lytic transcription comes from free genomes, starting at a viral promoter and ending at a viral terminator, whereas in transformed cells transcription can originate either at a viral or at a cellular promoter, often (but not always) ending at a viral terminator. A functional and a steric model are considered for activation of cellular functions. The study of mutations appears to support the functional model. The recent demonstration that a cellular function required for the expression of transformation by SV40 is not required by murine sarcoma virus suggests that different transforming viruses activate different parts of the host genome. (No refs)

151. ON THE PROBLEM OF ONCOGENE OF TUMOUR VIRUSES.

Mekler LB

Karamyshevskaya Naberezhnaya 50, kv. 5, 123448 Moscow, USSR

Acta Virol (Praha); 19:501-508 1975

The problem of the oncogenesis of tumorigenic viruses is described in relation to a general theory of oncogenesis and the Altshtein-Vogt hypothesis. The theory of oncogenesis claims that, after incorporation of the viral genome into the cell genome, the realization of the viral genetic information follows the laws governing the work of the cell genome; integration of the oncogene with the cell genome leads to transformation into a malignant cell. The Altshtein-Vogt hypothesis deals with oncogene origin and not with the mechanisms of benign or malignant transformation itself. It is concluded that an understanding of the oncogene position effect demonstrates that an integration of the genome of other viruses with the cell genome may lead to pseudoautoimmune disease or antiviral stable immunity. (27 refs)

152. INTEGRATION OF VIRAL DNA INTO THE HOST GENOME.

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Weyertal 121, W. Germany

Curr Top Microbiol Immunol; 71:1-78 1975

The integration of viral DNA into the host genome is discussed. Methods utilized to demonstrate integration of viral genomes (using bacteriophages and lysogenic cells) and the analysis of viral genomes in the chromosomes of eukaryotic cells are presented. Bacteriophage lambda, bacteriophage mu, adenovirus, simian virus 40 (SV40), polyoma virus, the adeno-SV40 hybrid viruses, herpes viruses, and RNA tumor viruses are described. Integration of viral DNA into host genomes is well-established in the bacteriophage systems. Among animal viruses, integration is documented for the SV40 and adenovirus DNA's and to a lesser extent for polyoma virus DNA. The persistence of the viral genome in virus-transformed cells is known. In substituted genomes of SV40, host DNA is covalently linked to viral DNA. (503 refs)

153. TUMOR VIRUSES: 1974. (PP. 1187-1200)

Baltimore D

Tumor Viruses Cold Spring Harbor Symposia on
Quantitative Biology, vol. 39, Cold Spring Harbor Lab.
(Cold Spring Harbor, NY, 1975).

Most of what is known about the RNA tumor virus can be codified by consideration of four genetic elements. Singly, these four genes (env, pol, gag, and onc) are responsible for the production of a protein that the virus uses to absorb cells, the encoding of the precursor to all major internal antigens of the virus, or the production of the protein of a sarcoma virus that is able to transform the growth property of cells. Most evidence strongly suggests that the genome of the RNA tumor viruses is a polyploid genome consisting of at least two identical subunits. Reverse transcriptase is the enzyme thought to be responsible for synthesizing the DNA copy of viral RNA. Once the viral DNA is integrated into the cellular DNA, it becomes a template for the synthesis of viral RNA. The synthesis of all viral proteins appears to be achieved by the synthesis of a polypeptide, a single chain of amino acids that must be cleaved to yield the functional proteins. The regulation of expression of the RNA tumor virus genome is not clear. The ability of RNA tumor viruses to become established in cells as integrated proviral DNA means that a cell can acquire a viral genome either by infection or by inheritance. Evidence for each pathway is reviewed. The current information on polyoma virus, adenovirus, herpesvirus, and Epstein-Barr virus was discussed in detail, including the concept of transformation.

154. FROM THE MOLECULAR BIOLOGY OF ONCOGENIC DNA VIRUSES TO CANCER.

Dulbecco R

Imperial Cancer Res. Fund Labs., Lincoln's Inn Fields,
London, W.C.2, England

Science; 192(4238):437-440 1976

The relationship between oncogenic DNA viruses and cancer is reviewed. Early studies showed that polyoma virus could be assayed in certain cell cultures (permissive) and could induce a cancerlike state in other cultures (nonpermissive), this induction being called transformation. Integration is one of the key events in virus-induced cell transformation. Cell genes play a continuing role in transformation, but the relationship between viral gene expression and cell phenotype is complex. Further progress came from studies of the proteins, the T-antigens in particular, specified by the early region of the viral DNA. Since the early, transforming part of the SV40 genome can specify proteins of a molecular weight of about 100,000

daltons, the T antigen is likely to be its sole product and, therefore, the transforming protein. Cellular events during transformation include functional changes and mutations, which are not well understood. Further knowledge of the mechanisms of growth regulation in animal cells is also necessary. The possibility that the viral transforming protein replaces one of the normal nuclear regulatory proteins of the cell is considered. For control of cancer it would be important to recognize the developmental period in which the anachronistic genes of transformed or cancer cells are normally expressed. Because of the persistence of viral DNA in the transformed cells, whether or not a given DNA is a possible agent of human cancer might be ascertained by looking for its DNA in the cancer cells. The feasibility of cancer prevention is indicated by the fact that promutagens already identified in preliminary screening (e.g. tobacco, some hair dyes) are inessential for human life.

155. VIRUSES, POLYMERASES, AND CANCER.

Baltimore D

Dept. Microbiology, Massachusetts Inst. Technology,
Cambridge, MA 02139

Science; 192(4240):632-636 1976

In this Nobel Prize lecture, the author reviews his work on the study of different genetic systems of RNA viruses. Early studies were concerned with picornavirus RNA production and the various enzymes involved, with poliovirus being the principal subject. Only three species of RNA are seen in poliovirus-infected cells, but with vesicular stomatitis virus (VSV), at least nine RNA's are produced, one of which is heterogeneous. The discovery of a virion polymerase in VSV led to the search for these enzymes in other viruses, particularly RNA tumor viruses. Two distinguishable time periods follow infection of a cell by a retrovirus: a period of reverse transcription and establishment of the DNA provirus as an integrated part of cellular DNA, and a period of expression of the integrated genome and synthesis of progeny virions. The biochemical events of each of these periods are summarized. Three kinds of explanations have been proposed for virus-related genes that are inherited in the germ line of so many animal species. The first is that they are an aspect of the animal and are virus-related because they are the progenitors of retroviruses. The second suggests that they are genes inserted into the chromosome of some ancestral animal by retrovirus infection of the germ cells of that animal. The third explanation, considered the most likely, is a modification of the second, in which any positive role for viral genes in the life of the infected animal is excluded.

156. LATENCY AND THE TUMOR VIRUS PROBLEM.

Harris RJ

Microbiological Res. Establishment, Porton Down,
Salisbury, Wiltshire, England

J Theor Biol; 62(2):287-298 1976

The condition of latency in virus-cell relationships is reviewed. In vitro cultivation of cells from animals infected with herpesviruses has led to virus activation in several instances. Numerous experiments providing evidence for the persistence of the viral genome in transformed cells are described. Some evidence has suggested that virus defectiveness may have a special role in transformation. Oncornaviruses produce cell transformation and induce tumors in cells/animals of species to which they are unnatural, but oncornaviruses function within their natural host and may show vertical transmission. Recent speculation about the evolutionary origin of oncornaviruses and their relationship to malignancy is discussed. Studies on the Epstein-Barr (EB) virus found in patients with Burkitt's lymphomas indicate that this viral genome may be nonintegrated and extrachromosomal. The condition in which virus associated

with the genome can occur without multiplication of either virus or cell may constitute latency. The release of latent viruses by simple culture of the tissue or organ has not been satisfactorily explained. In the presence of latent oncornavirus, viral RNA may produce a copy DNA (cDNA) that is then associated with the genome. Association or even integration of nucleotide sequences of DNA of originally infective origin may not be accompanied by cell multiplication, transformation, or malignancy. (83 refs)

157. VIRUSES AND MECHANISM OF CANCER. (PP. 357-366)

Dulbecco R

Host Environment Interactions in the Etiology of Cancer in Man. Doll R, Vodopija I, Davis W, ed. International Agency for Research on Cancer Lyon France, IARC Scientific Publications No. 7, 1976.

Developments in cell transformation research were applied to a discussion of the nature and origin of natural cancer. The following results of polyoma virus studies were reviewed: (1) oncogenic viruses transform cells mostly by bypassing the normal regulation of growth control; (2) the growth regulatory change of transformed cells is produced by a single viral gene whose product probably alters the function of the cell surface receptors; (3) a second viral gene causes integration of the viral DNA as provirus into cellular DNA and probably also detachment of the provirus; (4) the behavior of the provirus is determined by cellular genes; and (5) genetic transfer occurs between viral and cellular DNA and between different viral DNA's. These results may apply, with some adjustment, to all the oncogenic viruses. However, the mechanism of the co-oncogenic effect of leukemogenic viruses is probably entirely different and, so far, unknown. The etiological role of Epstein-Barr virus (EBV) is uncertain because it is widely distributed and the cancers in which it is implicated are rare; it cannot be excluded that EBV is just a passenger. Some features of the oncogene and provirus hypotheses of cancer etiology were included in a third hypothesis, which mainly assumes that a series of evolutionary events is initiated when a cellular regulatory gene is incorporated into a cyclic viral DNA. Free evolution would produce the transforming gene, which would then be selected for. If the transforming gene were latent in a cell, it would become activated without viral involvement by combining with an active part of the cell's own DNA; this would be classified as spontaneous cancer. When different viruses can transform the same cell, the proteins specified by the transforming genes of the viruses, and that specified by the corresponding normal cellular gene, should share some structural feature. This hypothesis provides an alternative to the classical mutational hypothesis for a genetic mechanism of cancer. (40 refs)

B. Reviews of Retroviruses and Their Proviruses

158. CANCER VIRUS THEORIES: FOCUS OF RESEARCH DEBATE.

Culliton BJ

No Affiliation

Science; 177(4043):44-47 1972

Three models currently dominate the field of viral oncogenesis in humans. The provirus hypothesis, introduced in the early 1960's, states that an RNA tumor virus infects a cell, which then incorporates the genetic information contained in the viral RNA into its own DNA and thereby acquires the capacity to produce an oncogenic virus and become transformed into a neoplastic cell. The viral genetic information is located at a single site on one chromosome. The integration takes place using a viral reverse transcriptase which makes a DNA copy of the viral RNA. According to the oncogene hypothesis, put forward in 1969, infection of cells by

C-type RNA viruses occurred millions of years ago. Every cell now contains an oncogene, a region of DNA that is normally repressed. Derepression of the oncogene by another virus, chemicals, or radiation results in production of a "transforming protein" which causes the cell to become malignant even though no viruses are produced. The provirus hypothesis, similar to the oncogene model, evolved in 1970 as a logical extension of the discovery of RNA-dependent DNA polymerase. This hypothesis holds that cancer viruses arise from proviruses - segments of genetic information randomly brought together through a variety of genetic events. The reverse transcriptase is also present in normal cells where it plays a role in differentiation. Recent evidence supports one or more of these models. Attempts to isolate a whole cancer virus from human tissues has resulted in a number of "candidate" viruses, including C-type and B-type. Molecular hybridization experiments have suggested that C-type virus information is present in human leukemias, lymphomas and sarcomas. A reverse transcriptase has been found in many leukemia patients and is associated with a high molecular wt RNA that is homologous to Rauscher leukemia virus RNA. The oncogene hypothesis has received support from experiments in which C-type viruses were induced in normal, supposedly virus-free cells. The ability of susceptible cell strains to be infected by their own virus is also consistent with the oncogene model since the oncogene would be derepressed in this state. The provirus model is supported by the finding of reverse transcriptase activity in normal embryo cells and in normal PHA-stimulated lymphocytes.

159. ONCORNAVIRUSES AND THEIR PROVIRUSES.

Bentvelzen P, Daams JH

Netherlands Cancer Inst., Amsterdam

Rev Eur Etud Clin Biol; 17(3):245-248 1972

The two prevailing theories of the "provirus", or viral agent supposed to give rise to neoplastic development in cells, are reviewed and a new hypothesis which reconciles the prevailing theories is presented. According to the "somatic provirus" theory, a virus infects a cell and proceeds to produce viral DNA by means of an RNA-dependent DNA polymerase. The viral DNA is integrated with host cell DNA which it alters to code for neoplastic conversion. According to the "germinal provirus" theory, the provirus genetic information is present in a host chromosome from the outset (no infection event is postulated) and is transmitted genetically to the offspring. No RNA-dependent DNA polymerase is required for virus continuity. Mutation, aging or carcinogenic stimuli cause the germinal provirus genetic information to be expressed, leading to cancer. In noncancerous cells, the germinal provirus is ordinarily repressed, possibly by some form of the classical repressor molecule. A new concept postulates that carcinogenic stimuli temporarily derepress a germinal provirus, which produces some viral RNA. This RNA produces a viral DNA by means of a reverse transcriptase (as in the somatic provirus) and this DNA becomes integrated into host cell DNA, but at a locus which is not affected by repressor molecules. Unsuppressed, the viral DNA produces DNA which codes for neoplastic change.

160. ECOLOGICAL GENETICS OF RNA TUMOR VIRUSES AND THEIR HOSTS.

Weiss RA

Imperial Cancer Res. Fund Labs., London, England

Proc Third Int Symposium Princess Takamatsu Cancer

Res Fund. Japan; 201-233 1973

RNA tumor viruses are endemic in many species of animals. They are transmitted from one host to another via: horizontal infection by contact or proximity; congenital infection from mother to offspring; and genetic transmission from either parent in the form of DNA proviruses integrated

into the chromosomes of the gametes. The infectious modes of transmission are subject to host range barriers which are genetically determined by the host. While a single Mendelian gene has an overriding influence on host susceptibility to infection in both mice and chickens, resistance is dominant in mice but recessive in chickens. The ecological genetics of the RNA tumor viruses and their hosts are viewed in relation to the different modes of transmission and host range controls operating in natural populations. The interactions between different kinds of RNA tumor virus are also viewed in relation to their natural history. None of the various models concerning the natural history of the RNA tumor viruses in animal populations appears to be singularly appropriate to human cancer, although this may reflect differences in the genetic structure of human and animal populations rather than a fundamental difference in the etiology of cancer.

161. INPUT AND OUTPUT OF GENETIC MATERIAL IN CELLS PRODUCING C-TYPE RNA VIRUSES.

Hill M

Dept. Cell and Molecular Biol., Inst. Cancer, Immunogenetics, Villejuif, France
Biomedicine: 18(6):453-458 1973

Available evidence concerning the interaction between the genome of an RNA tumor virus and that of infected cell is reviewed. Infectious viral particles contain RNA-dependent DNA polymerase which transcribes viral RNA to DNA. In infected cells, the DNA complementary to a portion or to an entire viral genome becomes integrated into the cellular genetic material and can be shown to be infectious proviral DNA by its capacity to infect permissive cells. It appears, however, that even uninfected cells contain the endogenous C-type virus genome (perhaps identical with DNA sequences hybridizing with viral RNA *in vitro*) which can be activated upon induction to give rise to C-type particles. Further data are required in order to understand the interactions of oncogenic viruses in animal cells in greater depth.

162. GENETIC FACTORS IN THE NATURAL HISTORY OF MURINE LEUKEMIA VIRUS INFECTION: G.H.A. CLOWES MEMORIAL LECTURE.

Rowe WP

Natl. Inst. Hlth., Bethesda, Md.
Cancer Res: 33(12):3061-3068 1973

The history of tumor virology consists of four stages, the last of which has been characterized by the concept that tumor viruses are an integral part of the host. An oncogene theory to explain the expression patterns of the murine leukemia viruses (MuLV) holds that the viral genetic material is present in normal cells, that it can be expressed as infectious virus or only as viral antigens without production of virus, and that the noninfectious expression of a protein of the viral genome may be responsible for the cellular alteration leading to cancer. Studies of the MuLV in the AKR mouse revealed that the complete viral genome is an integral, heritable component of all AKR cells, that it can be present in unexpressed form, and that it does not render the cells resistant to superinfection by the same virus. Genetic and progeny studies showed that the MuLV genome is a heritable component of AKR cells and that its presence or expression in hybrids is genetically controlled. The AKR possesses two unlinked, presumably identical virus loci, and there is some indication that the virus-inducing loci are the structural genes of the virus. The virus-inducing loci are relatively stable and preliminary findings suggest that the viral genomes are not inserted at allelic sites in different strains. Present evidence indicates that MuLV genomes are chromosomally located, with at least three genes being involved in the etiology of AKR lymphoma.

163. THE BERTNER FOUNDATION MEMORIAL AWARE LECTURE-FROM PROVIRUSES TO PROTOVIRUSES: RNA-DIRECTED DNA SYNTHESIS BY RNA TUMOR VIRUSES AND CELLS.

Temin HM

McArdle Lab. Cancer Res., Univ. Wisconsin, Madison
Collect Pap Annu Symp Fundam Cancer Res: 25:7-38 1974

The histories of the DNA provirus and provirus hypotheses are reviewed. The present status of the evidence for these hypotheses is discussed, including the recent finding of an RNA-directed DNA polymerase activity in normal chicken cells. The DNA provirus hypothesis states that replication of Rous sarcoma virus (RSV) involves formation of a DNA intermediate, which then replicates by DNA-DNA information transfer when cells replicate and by DNA-RNA transfer when progeny virus is formed. Critical evidence in favor of the hypothesis could come from confirmation of experiments indicating that an infectious DNA which contains information for RSV can be isolated from RSV-infected mammalian cells. RSV replication and transformation involve steps other than the synthesis of the DNA provirus, the intermediate for virus replication that contains the genes for virions and for transformation. Problems concerned with these other steps are discussed: specifically, the control of virus RNA synthesis, the origin of variants, the origin of virion DNA polymerase, its relationship to cell polymerases and the question of other enzymes in virions. The discovery of an RNA-directed DNA polymerase activity in normal cells, as predicted by the provirus hypothesis, suggests some of the possible biologic effects of proviruses (nonintegrated and integrated). These might include gene amplification, gene removal to a different location and variant sequences. Other biological consequences could be the origin of genes for neoplastic transformation, the origin of induced leukosis-like viruses and, if altered provirus DNA were integrated in germ-line DNA, the origin of genetically altered progeny. Although laboratory RNA tumor viruses are unlikely to be implicated in human neoplasia, it is possible that RNA tumor virus-related information is related to human neoplasia and that carcinogens act on provirus information transfers to alter normal cellular information to create the genes for neoplastic transformation.

164. MOLECULAR EVIDENCE FOR VIRAL AGENTS IN HUMAN CANCER AND ITS CHEMOTHERAPEUTIC CONSEQUENCES.

Spiegelman S

Inst. Cancer Res. Coll. Phys. Surg., Columbia Univ., New York
Cancer Chemother Rep: 58(4):595-613 1974

Sequence homology between virus and cellular nucleic acids was studied. Homology exists between myeloblastosis and Rous sarcoma virus (RSV), and between murine leukemia and murine sarcoma viruses (MuLV, MuSV, respectively), although murine mammary tumor virus (MMTV) was unique. Human tumor cells were examined by DNA/RNA hybridization techniques, using viral-specific labeled DNA. Homologies were found between human mammary and MMTV nucleic acids and between human leukemia, lymphoma, and sarcoma and RLV nucleic acid. The cytoplasmic RNA from 21 patients with Burkitt's lymphoma contained sequences homologous with RLV in 76% of cases, but there was no homology with MMTV. A simultaneous detection test for high molecular wt viral RNA and reverse transcriptase was described. The application of this test to 38 patients with adenocarcinomas gave 74% positive results, yielding an RNA density characteristic of oncogenic viruses. The peripheral leukocytes of 23 leukemic patients contained virus-like particles in over 95% of cases, although none of 18 non-leukemic controls contained these

particles. In 70% of Hodgkin's disease patients, 82% with Burkitt's lymphoma, and 88% of patients with other cancers (including lymphosarcomas and reticulum cell sarcomas), these virus-like particles were detected. The virus-like particles had a buoyant density of 1.16-1.19 g/ml, and contained 70S RNA associated with reverse transcriptase. The malignancy DNA was shown to be absent from the germ lines of normal human cells, and normal DNA did not complex with lymphoma ³H-DNA. The DNA from 2 leukemic identical twin pairs contained 70S particles homologous with virus-like material but absent in the cells of their normal healthy twins. Hence, the malignant transformation requires the insertion of viral-related information, and raises the possibility of pre-disease clinical diagnosis by hybridization technic. (33 refs)

165. RNA AND DNA FORMS OF THE GENETIC MATERIAL OF C-TYPE VIRUSES AND THE INTEGRATED STATE OF THE DNA FORM IN THE CELLULAR CHROMOSOME.

Hill M, Hillova J

Inst. Oncol. Immunogenetics, Villejuif, France

Biochim Biophys Acta: 355(1):7-48 1974

Literature pertaining to lines of evidence concerning the RNA and DNA forms of the virus genome of C-type viruses is reviewed. The nucleic acid composition of the C-type RNA viruses is discussed in terms of the denaturation and structure of fast-sedimenting RNA, the 4-S and 7-8-S slow-sedimenting RNA species, DNA, and attempts to define the viral genome. Evidence is then presented which suggests that a DNA intermediate is involved in the replicative cycle of C-type RNA viruses. This is defined in its relation to requirement for early DNA synthesis, continued requirement for DNA-dependent RNA synthesis, the occurrence and purification of viral reverse transcriptase and the presence of virus-specific base sequence in the DNA of normal and infected cells. The infectious proviral DNA in animals' cells infected with C-type RNA viruses is considered in terms of the uptake of foreign DNA by animal cells in vitro, the fate of foreign DNA in chicken cells, virus recovery in chicken cells treated with Rous sarcoma cell DNA, endogenous C-type RNA viruses in chicken cells, the envelope properties of viruses recovered with infectious proviral DNA, the transformation capacity of viruses recovered with infectious proviral DNA, the infectivity of double- and single-stranded forms of Rous sarcoma cell DNA, the integration of infectious proviral DNA in the cellular chromosome, and the competence of recipient cells in the occurrence of infectious proviral DNA. A model is proposed for virus replication and interaction with the cellular chromosome; this model takes into account new experimental data which is not compatible with previous concepts.

166. VIRUSES AND HUMAN CANCER.

Spiegelman S

No affiliation given

Prog Hematol : 9:305-330 1975

Experiments to obtain evidence of viral etiology for some human cancer are reviewed. DNA-RNA hybridization was used to determine whether human tumors contain viral-related RNAs. Human breast cancer contained RNA homologous to that of the murine mammary tumor virus (MMTV); human leukemias, sarcomas, and lymphomas all contained RNA with sufficient homology to that of the murine leukemia virus (RLV) to make a stable duplex. The pattern of the unique RNA found in the human neoplasias was in complete agreement with what had been found for the corresponding viral-induced malignancies in the mouse. The simultaneous detection test established that at least a portion of the tumor-specific virus-related RNA detected in human breast cancer and leukemia was a 70S RNA template physically associated with a reverse transcriptase in a particle possessing a density

between 1.16-1.19 g/ml, three of the diagnostic features of the animal RNA tumor viruses. The DNA synthesized in the particles from both breast cancer and leukemia hybridized uniquely to the RNA of the corresponding oncornavirus. Recycling hybridization experiments indicated that leukemic cells, and those from Hodgkin's and Burkitt's lymphoma, contain unique sequences not seen in normal cells. In studies conducted with two sets of identical twins, one member of each set having leukemia, a sequence difference was established between the identical twins implying that the additional information found in the DNA of the leukemic member of the set was inserted after zygote formation. This finding argues against the applicability of the virogene hypothesis to this disease, since it demands that the leukemia-specific sequences found in the DNA of the diseased individual must also exist in the genome of his identical twin. The presence of unique sequences in malignant DNA is not consistent with any mechanism for cancer induction that does not involve the insertion of viral-related sequences into the DNA of malignant cells. Further, the identical twin data require the postzygotic insertion into the genome of the viral information, a process known to occur with RNA tumor viruses in animal cells. (44 refs)

167. EVOLUTION OF PRIMATE TYPE-C VIRAL GENES. (PP. 29-53)

Benveniste RE, Sherr CJ, Lieber MM, Callahan R, Todaro GJ

Fundamental Aspects of Neoplasia. Waksman Institute of Microbiology of Rutgers University, New York, 424 pp., 1975.

Studies relating to the evolution of primate type C viral genes are reviewed. ³H-DNA transcripts prepared from three baboon type C virus isolates hybridized completely to DNA extracted from tissues of various baboons, suggesting that these type C viruses are endogenous viruses of the baboon. A DNA reassociation experiment was performed using a ³H-DNA transcript of baboon type C virus and DNA extracted from various primate species. The baboon type C viral DNA probe detected homologous nucleic acid sequences in all the Old World monkeys examined; the degree of homology of the virogene sequences closely correlated with the taxonomic relatedness of the monkey species. No homology was detected in various New World monkey DNAs. These findings suggest that the virogene sequences have been highly conserved during evolution and have evolved as cellular entities diverging from one another in the different genera and species in a manner consistent with a common ancestry and their presence in the ancestral primate germ line. DNA sequences partially homologous to the endogenous baboon type C virogenes were also detected in the genome of the domestic cat, and baboon type C viral RNA has been shown to be partially homologous to the viral RNA of the RD114/CCC group of endogenous domestic cat viruses. No other mammalian type C viruses (including another cat virus) have been shown to hybridize to the baboon viral ³H-DNA probe. Studies with other feline species suggest that domestic cat viruses of the RD114/CCC group originated, 5 to 15 million yr ago, from an exogenous infection of progenitors of domestic cats by a type C virus that also gave rise to the present day endogenous type C viruses of Old World monkeys. The data suggest that viral genes from one group of animals can give rise to infectious particles that can not only integrate into the DNA of animals of another species, but can also be incorporated into the germ line. This viral transfer of nucleic acid sequences between distantly related species may be one mechanism by which species acquire new genetic information. (34 refs)

168. THE STRATEGY OF RNA VIRUSES. (PP. 57-74)

Baltimore D

The Harvey Lectures. New York, Academic Press Inc, Series 70, 1976.

A comparison is made of the following three types of superficially similar animal viruses: picornaviruses, typified by poliovirus; rhabdoviruses, typified by vesicular stomatitis virus (VSV); and RNA tumor viruses. The virions of all three contain a single strand of RNA that is 2.5 to 4 x 10⁶ daltons long, but their modes of replication are extremely different. The key observations that have initiated an understanding of each of the viral systems include: (1) the observation that poliovirus is infectious; its replication system is very simple since the virion RNA and messenger RNA (mRNA) are identical. (2) In VSV, the mRNA found on the polyribosomes was not the 4 x 10⁶-dalton virion RNA, but rather a collection of smaller complementary RNA's. (3) The viral genome in RNA tumor viruses contains reverse transcriptase, a primer-dependent DNA polymerase that makes a DNA copy of the viral RNA. This enzyme easily copies polyribonucleotides, contains ribonuclease H activity that can degrade the RNA portion of the DNA-RNA hybrid, and has a specific binding site for transfer RNA^{Trp} that is utilized for the initiation of copying the 70S RNA. The life cycle of RNA tumor viruses is illustrated. This cycle provides a mechanism of infectious spread from cell to cell or animal to animal. Because the provirus DNA is integrated into cellular DNA, spreading of virus by inheritance is possible. The two lytic viruses, polio and VSV, which must continually infect to propagate, sharply contrast with the integrative RNA tumor viruses that act as DNA to get into the animal's genetic system. (62 refs)

169. GENETIC TRANSFORMATION OF ANIMAL CELLS WITH VIRAL DNA OF RNA TUMOR VIRUSES.

Hill M, Hillova J

Dept. Cellular and Molecular Biology, Equipe de Recherche No. 148 du C.N.R.S., Inst. Cancerology and Immunogenetics, Villejuif, France
Adv Cancer Res; 23:237-297 1976

Experiments showing that animal cells become genetically transformed in vitro following infection with RNA tumor viruses are discussed. Infectious forms of the type C RNA tumor viruses carry an RNA-directed DNA polymerase, which, early in infection, transcribes viral RNA into DNA, the latter becoming covalently bound to the host cell chromosome. Transfection has shown that there is a DNA intermediate in the life cycle of the RNA tumor viruses that is integrated into the cellular genome. It is not clear whether the RNA-DNA and double-stranded DNA forms isolated in early infections are all precursors of the integrated viral DNA. It is possible that virus-infected cells contain, besides full-length viral DNA, partial transcripts that may escape detection in transfection assays. The integration mechanism inserting viral DNA into the cellular chromosome also remains unknown. The ability of both the sarcoma and leukemia viruses to cause malignant transformation depends on the presence of new genetic material, introduced by the virus into the infected cell, which can be detected by both nucleic acid hybridization and transfection. The viral genetic material of sarcoma viruses contains transforming genes that must be continually expressed to maintain the transformed phenotype of virus-infected cells. These transforming cells are not involved in virus replication. It is probable that these genes were originally mutated cell genes whose covalent linkage to viral nucleic acid sequences was favored by strong selection and passage in the laboratory. No temperature-sensitive (ts) leukemia virus mutants have yet been found that pinpoint transforming genes. Leukemia viruses almost certainly lack transforming genes found in sarcoma viruses, and it is possible that the

genes responsible for at least certain leukemias are also involved in virus replication. It is not clear whether endogenous viruses represent a natural reservoir for accidental evolution of exogenous viruses, or whether endogenous and exogenous viruses diverge early in evolution. Some oncogenic type C viruses lack genetic relatedness to their natural hosts, and no endogenous counterparts of these viruses have so far been identified. It is possible that certain animal tumors (including human leukemias) are due to products coded for by transforming genes of exogenous RNA tumor viruses. (305 refs)

170. THE SLOW INFECTION CAUSED BY VISNA VIRUS.

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Curr Top Microbiol Immunol; 72:102-156 1976

A view of visna virus infections is presented. The virus causes an inflammatory destructive disease of the sheep CNS, which results in demyelination and progressive neurologic disability. The prolonged incubation period and protracted clinical course make visna a prototype of slow infections. The virus is closely related to RNA tumor viruses in morphology, morphogenesis, and a number of biochemical properties. There is an association between visna virus and an RNA-directed DNA polymerase that transcribes the RNA genome of the virus into a DNA replica or provirus. The visna provirus is, at least in part, integrated into the host-cell genome. It is hypothesized that existence of the provirus provides a satisfactory resolution to one of the central issues of slow infection, persistence of virus in the face of the inflammatory and immune responses mounted by the host. Speculations about two major unresolved questions, the slowness of the disease and the nature of the tissue lesions, point to areas of significant future research. There is evidence that slowness results from the pace of provirus activation or from altered gene regulation in vivo that minimizes virus production. Direct and indirect mechanisms of cell damage may exist, both of which are related to the insertion of viral components into the membrane of the infected cell. In direct mechanisms, the membrane is damaged and the cell dies (CNS) or fuses (in vitro). The indirect mechanism proposed is that virus components elicit a cellular immune response attended by cell destruction (immunopathology). (232 refs)

171. PROSPECTS FOR BIOLOGIC AND PHARMACOLOGIC INHIBITION OF RIBONUCLEIC ACID TUMOR VIRUSES.

Smith RG, Gallo RC

Lab. Tumor Cell Biology, Natl. Cancer Inst., Bethesda, MD 20014

Biochem Pharmacol; 25(5):491-495 1976

Leukocytes from patients with acute myelogenous leukemia contain RNA virus that is similar to the woolly monkey sarcoma virus. The life cycle, replication, and mechanisms of transformation of these tumor viruses are discussed as possible sites of viral inhibition by biological and pharmacological inhibitors. The transcription of proviral DNA from viral genomic RNA is a prime target for inhibition since this pathway of information transfer is not known to occur in normal cells. Integration of viral DNA, synthesized by viral reverse transcriptase, into the host genome can be blocked with ethidium bromide, thus blocking transformation of cells and viral production. Viral RNA is synthesized by transcription of proviral DNA, and once initiated continues in stationary as well as dividing cells. Therefore, to inhibit naturally occurring oncogenesis in animals, the role of the virus in replication and transformation must be elucidated. The strategy of interference with oncogenesis depends on host-

virus relationships that vary depending on the species studied. No selective, potent pharmacologic inhibitors of any viral functions have been found. Most of the inhibitors that have been described are toxic to cells or animals. The authors discuss the feasibility of viral inhibition at various stages in animal and cell life-cycles and the treatments that are currently used for viral inhibition. They conclude that these treatments, with the exception of a rifamycin derivative, are not specific and therefore interfere with cellular functions.

172. TYPE C VIROGENES: GENETIC TRANSFER AND INTERSPECIES TRANSFER.

Todaro GJ

Natl. Cancer Inst., Bethesda, MD 20014

Adv Pathobiol; 4:38-46 1976

Studies of the genetic and interspecies transfer of type C virogenes are reviewed. Activation of normally repressed genetically transmitted type C virogenes information, rather than infection from outside the animals, was proposed as the most common mechanism by which type C RNA tumor viruses are maintained in animal populations and produce naturally occurring cancers. Implications of the virogenes-oncogene hypothesis are that all somatic cells of a species have DNA homologous to type C virus RNA of that species and that type C viruses derived from closely related species should have closely related gs antigens. Normal cellular DNA should contain transformation specific sequences of RNA tumor viruses, and spontaneous, chemically induced, and viral induced transformed cells and tumor cells should have RNA as well as DNA sequences homologous to the transforming specific sequences found in tumor viruses. The major differences between the virogenes and provirus models are discussed. Hybridization studies using endogenous baboon type C viral DNA indicated that sequences related to those of the baboon type C virus are present in all other Old World monkey species, higher apes, and in man. This supports the conclusion that in the primates, type C viral genes have evolved as the species have evolved, with virogenes from more closely related genera and families showing more sequence homology than those from distantly related taxa. Viral genes from one group of animals can give rise to infectious particles that can not only integrate into the DNA of animals of other species, but can also be incorporated into the germ line. Humans, like other primates, have type C sequences in their genome, and can, in some circumstances, express at least one type C viral protein. The possible role of viruses as natural transmitters of genes between species is discussed.

173. SOME ILLUSTRATIVE SYSTEMS OF VIRAL CARCINOGENESIS: THE FELINE LEUKAEMIA VIRUS. (PP. 393-403)

Jarrett WF

Scientific Foundations of Oncology. Symington T, Carter RL, ed. Chicago, William Heinemann Medical Books Ltd, 1976.

Feline leukemia virus (FeLV), which causes a wide range of hematopoietic tumors, is a useful model since both man and cat are randomly outbred species. The following three practical developments in FeLV have appeared recently: (a) FeLV infection is transmitted horizontally in urban cat populations where mixing of animals is frequent. (b) Many exposed cats develop immunity through antibody production (which has facilitated production of an effective experimental vaccine). (c) Several other nonneoplastic conditions are caused by FeLV, including various anemias, glomerulonephritis, fetal reabsorption and abortion, and a predisposition to infection due to immunodepression. Observations by electron microscope reveal that FeLV undergoes a budding process that is unique to oncornaviruses - ie, oncogenic RNA viruses whose genome is single-stranded RNA. Endogenous feline

oncornaviruses (eFOV), which have not been proved oncogenic, are morphologically indistinguishable from FeLV and may be transmitted vertically. The two major nucleic acid components of FeLV include a rapidly sedimenting 70S RNA and a more slowly sedimenting 4S RNA. The six major proteins in FeLV include four polypeptides, designated P10, P12, P15 and P30, and two membrane glycoproteins, GP35 and GP75, which seem to be the receptors for cell infection. Since oncornaviruses possess reverse transcriptase (an RNA-dependent DNA polymerase), vertical transmission may involve integration of provirus into host cell DNA, leading to infection of germ cells and hence infection of every cell in the member of the next generation. Studies involving the "feline oncornavirus-associated cell membrane antigen" (FOCMA) system have shown a surprisingly high percentage of urban cats with FeLV antibodies. Thus, although tumor incidence is low (approximately 0.05%), the incidence of exposure is high (up to 70%). In the pathogenesis of feline leukemia, whether or not the virus causes immunodepression before the production of moderately high levels of FOCMA antibodies depends experimentally on the dose of the virus. (22 references)

174. STRUCTURE OF THE INTERMEDIATES LEADING TO THE INTEGRATED PROVIRUS.

Weinberg RA

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Biochim Biophys Acta; 473:39-55 1977

Current knowledge of the mechanisms by which retroviruses transfer their genetic information from the single-stranded RNA of their virions to a double-stranded DNA linked to the cellular genome is surveyed. It is believed that in vivo reverse transcription of the single-stranded RNA begins near the 5'-end, progresses a short distance to the 5'-end, and then continues at the 3'-end of the same or another RNA subunit. This association of the initially synthesized DNA with both ends of the RNA template may lead to a transient circular form, the ends of the RNA being linked by DNA. The consequence of these initial steps is a DNA molecule, of length comparable to the viral genome, which may only have a transient association with the RNA on which it was synthesized. By unknown mechanisms, a double-stranded linear DNA molecule of full genome length is next synthesized. This form of the DNA is infectious and may have "sticky ends", in that it appears to circularize at high ionic strength. It may be the immediate precursor of the integrated form of the virus. (84 Refs)

175. CONCEPTS ON THE INTERFERENCE OF REPLICATION AND EXPRESSION OF RNA TUMOR VIRUSES.

Gillespie D, Gallo RC

Lab. Tumor Cell Biology, NCI, NIH, Bethesda, MD 20014
Ann NY Acad Sci; 284:576-584 1977

A discussion is presented of factors involved in the infection and expression processes of human cancer, especially as they influence conceptualizing chemical treatment. The biochemical event in the infection process that is most specific to RNA tumor viruses is where DNA free provirus copies of the infecting viral RNA are made via the RNA-dependent DNA polymerase (reverse transcriptase or RT). This step was predicted to be most amenable to chemotherapeutic manipulation, but this may not be so, since an anti-RT agent (or anti-infection agent) has an effect only on very early events in tumor formation (whether transformed cell proliferation with or without recruitment). These events occur before the tumor is detectable and such an agent would probably not be useful for control of an established tumor, although RT inhibitors may be valuable in remission maintenance therapy. For control of an established malignancy, ways of altering the expression or the consequence of expression of virogenes or

integrated proviruses must be found. A biochemical event in the expression of viral genes that may be altered is related to events in processing the RNA transcripts of viral genes, termed RNA paraprocesing. RNA from RNA tumor viruses undergoes less nuclear cleavage so that the resulting RNA molecules are larger, and viral RNA may be cytoplasmically polyadenylated. It is suggested that 3'-deoxyadenosine and other inhibitors of polyadenylation should be examined for their antitumor effects in animals. Other antitumor effects are seen in chickens, mice, and cats carrying virus-induced tumors: antibodies prepared against antigens found on the surface of tumor cells (TSTA antigens in chickens and mice and FOCMA antigen in cats) are cytotoxic, kill the tumor cell, and can control tumor growth. There is no correlation between the presence of tumors and virus levels in cats; what is important is the ratio of FOCMA antibody to tumor cells. Similar tumor-specific antigens should be sought in humans. (21 Refs)

176. THE DNA PROVIRUS HYPOTHESIS. THE ESTABLISHMENT AND IMPLICATIONS OF RNA-DIRECTED DNA SYNTHESIS.

Temin HM

McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI 53706

Science; 192(4244):1075-1080 1976

The observations and experiments that have led to the formation and establishment of the provirus hypothesis and the DNA provirus hypothesis are discussed. This discussion includes RNA-directed DNA synthesis for the formation of the provirus. The mechanisms of formation of the DNA provirus that were known through November of 1975 are briefly reviewed. Hypotheses for the origins of ribodeoxyviruses and the origins of other animal envelope RNA viruses or small DNA animal viruses are proposed. Infectious viruses probably do not cause human cancer. In fact, RNA tumor virus replication is not sufficient for cancer formation by RNA tumor viruses. It is suggested that the targets for the non-viral carcinogens are the genes involved in information transfer from DNA to RNA to DNA. Thus, genes for cancer would be formed in a process involving RNA-directed DNA synthesis in both RNA virus-induced and nonvirus carcinogen induced cancers. (67 refs)

C. Reviews of Papovaviruses, Adenoviruses and Herpesviruses and Their Integrated Genomes

177. THE INVESTIGATION OF ONCOGENIC VIRAL GENOMES IN TRANSFORMED CELLS BY NUCLEIC ACID HYBRIDIZATION.

Winocur E

Weizmann Inst. Sci., Rehovot, Israel

Adv Cancer Res; 14:37-70 1971

This report accentuates those aspects considered relevant to the understanding of the role of viral genes in transformed cells. The central issue dominating current thinking on the mechanisms of viral carcinogenesis concerns the presence, the state, and the role of viral genetic material in the transformed cell. Several lines of evidence point to the persistence of viral genes in all transformed cells and their descendants. Viral DNA sequences in the DNA of transformed cells are discussed in light of hybridization procedures utilized for the detection of viral DNA sequence, the number and state of the viral genomes, the homology between SV40 and cell DNA, and the integration of the viral DNA. With the evidence for the viral DNA established, the transcription of the viral genome with particular reference to the identification and control of viral gene activity is considered. The coding potential, quantity, location and size of viral mRNA in transformed cells are discussed. A technique for determining the proportion of the viral genome by competitive hybridization between two viral

mRNA's is detailed and tables summarizing the estimates reported by several investigators are given. The difficulties which persist in establishing the common sequence in viral mRNA's from productively infected and transformed cells are presented. Recent experiments indicating a possible common basic feature in the mode of action of both DNA-containing and RNA-containing tumor viruses are presented as a challenge to tumor virologists who must face the task of formulating fundamentally similar mechanisms to account for oncogenic action.

178. TRANSFORMATION BY POLYOMA VIRUS AND SIMIAN VIRUS 40.

Sambrook J

Cold Spring Harbor Lab., N.Y.

Adv Cancer Res; 16:141-180 1972

Experiments that bear on the mechanism by which virus transformation occurs and the ways currently being used to isolate and characterize those virus proteins responsible for the phenomenon are reviewed. Polyoma virus and Simian virus (SV) 40 are viruses of simple structure and contain enough DNA to code for only a few proteins. About 12% of these two viruses is DNA; the rest is protein. This framework supports a variety of complicated interactions with cells, one of which is transformation, where virus infection causes the cells to assume malignant properties. At least one virus-coded function is necessary to establish transformation, and integrated viral DNA persists in the transformed cells. Although this integrated DNA may be necessary to provide for the genetic stability of the transformed state, it is not of itself sufficient to cause expression of the transformed phenotype, for which additional virus-coded functions are required. Most current research on polyoma virus and SV40 is directed toward cataloguing and identifying these functions.

179. INTEGRATION OF VIRAL DNA IN TRANSFORMED CELLS.

Blancy D, Dulbecco R, Haas M, Vogt M

Salk Inst. Biol. Stud., San Diego, Calif.

Collect Pap Annu Symp Fundam Cancer Res; 25:427-439 1974

Results of experiments to determine the number, location and physical state of viral genomes in cells transformed by oncogenic DNA viruses are summarized. The topics covered are: quantitation of viral DNA in transformed cells by DNA-RNA hybridization or by DNA reassociation kinetics, evidence for integration of the viral genome in cellular DNA, rescue of viral DNA from transformed cells, rescue by exposure to chemical or physical agents, induction of polyoma in Tsa-transformed 3T3 cells, viral genes in integration and excision, transcription of integrated viral genome, and occurrence of lytic integration. The experimental findings show that viral DNA is covalently associated with host-cell chromosomes and is probably transcribed as a large heterogeneous messenger RNA containing both viral- and cellular-specific sequences. Integration, has important consequences for the virus: it allows the replication of the viral DNA together with the cellular DNA, without using viral functions, it causes the cotranscription of viral and cellular DNA, placing the viral DNA under the genetic regulatory control of the cells and it permits the incorporation of cellular DNA into viral DNA. Integration also has consequences for the cells. Not only does it make the transformed state permanent, but it may contribute to determining transformation by interrupting the normal regulatory connections of the cellular genes.

180. INTEGRATION OF VIRAL DNA INTO THE HOST GENOME.

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Curr Top Microbiol Immunol; 71:1-78 1975

The integration of DNA of animal viruses into the host genome is reviewed, as are selected topics dealing with lysogeny and the temperate bacteriophages λ and Mu. In the case of phage λ , there is a phage-encoded, highly efficient recombination system that leads to the insertion of the phage DNA into the bacterial chromosome at one specific site. Bacteriophage Mu integrates its DNA into the host genome randomly and causes polar mutations at the site of insertion. Integration has been well-documented for the adenovirus and simian virus 40 (SV40) DNA's and to a lesser extent for polyoma virus DNA. Evidence has also been presented for the covalent insertion of the reverse transcripts of tumor virus RNA, particularly in Rous sarcoma, avian myeloblastosis, and murine leukemia virus systems. Complete copies of type C virus DNA have been found in the somatic cell DNA of the chicken, Chinese hamster, Syrian hamster, mouse, rat, cat, pig, and baboon. The integration site of viral genes has been localized on a specific chromosome of eukaryotic cells in only one instance: SV40 DNA can become associated with human chromosome C-7. In human cells infected with adenovirus type 12, a specific break on chromosome 17 close to the thymidine kinase locus has been reported, but there is no evidence that the site is identical with the site of integration. Integration of viral genetic material in transformed cells has been shown in SV40-transformed cells and in cells transformed by RNA tumor viruses. In most cases of virus-transformed cells, the persisting viral genes continue to be transcribed and virus-specific messenger-RNA, frequently of high molecular weight, is found associated with the polysomes, indicating that viral genes are translated in transformed cells.

181. MAPPING VIRAL INTEGRATION SITES WITH SOMATIC CELL HYBRIDS.

McDougall JK

No affiliation given

Nature (Lond); 256(5516):364-365 1975

Studies with SV40-transformed human cells hybridized with thymidine kinase-negative mouse cells are reviewed. These studies led to the conclusion that the gene(s) responsible for transformation and the integrated SV40 genome are located on (human chromosome) C7. Other work with SV40-transformed mouse cells and adenovirus-transformed cells is also reviewed. It is suggested that somatic cell hybridization techniques are now a method of choice for localizing integrated viral sequences.

182. INTEGRATION OF DNA TUMOR VIRUS GENOMES.

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Health, Bethesda, MD 20014

Curr Top Microbiol Immunol; 73:35-65 1976

Controlled hybridization analyses are the most direct approach for demonstrating the integration of viral DNA sequences within the host genome. Evidence for the continued presence of viral DNA in simian virus 40 (SV40) transformed cells was first obtained in virus-rescue experiments; data indicated that the induction mechanism requires fusion of the virus-free transformed cell with the permissive cell. Integrated viral genetic information can be detected by procedures utilizing separated strands of viral DNA, an analysis of DNA reassociation kinetics, or reconstruction and calibration experiments. Since infectious SV40 can be recovered from

virus-free transformed cells by cocultivation or fusion with permissive African green monkey cells, the viral genome is probably present in a latent form. Findings from experiments on SV40 genome equivalents in transformed cells suggest that a single copy of SV40 DNA is sufficient to transform a cell. The presence of multiple copies of viral DNA in transformed cell lines cannot be correlated with any phenotypic difference or the amount of virus-specific RNA present. Although viral DNA can be detected in several virus-free transformed cells, the physical relationship of the viral genome to host cell DNA has not been fully resolved. Most reports concerning the relationship of papovavirus and adenovirus DNA's to cellular DNA suggest that viral DNA is integrated into the cell genome. Recent studies with temperature-sensitive mutants of SV40 suggest that a viral gene product is necessary for continued maintenance of the transformed state.

183. THE BIOLOGY AND SEROLOGY OF EBV INFECTIONS.

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Bull Cancer (Paris); 63(3):399-410 1976

The Epstein-Barr virus (EBV), carried by the majority of the world's adult human population, is closely associated with three known human diseases: infectious mononucleosis (IM), Burkitt's lymphoma (BL) and nasopharyngeal carcinoma (NPC). It is now generally accepted that EBV plays an active role in the etiology of BL and NPC rather than simply being a "passenger". Considerable evidence also argues for the participation of co-factors in these two diseases. Environmental co-factors appear needed to explain the peculiar geographical distribution of BL. Among various possibilities that must be considered are insect-transmitted agents that could lead to eventual immunosuppression and/or stimulate further proliferation of EBV-transformed cells, thereby permitting an additional cytogenetic evolution towards malignancy. Recent studies have uncovered a possible cytogenetic co-factor in the etiology of BL: the 8-14 chromosomal translocation. Genetic co-factors, on the other hand, are likely to be involved in the etiology of NPC. EBV is a B-cell associated virus. Carrier lymphoid cell lines obtained either by *in vitro* "immortalization" of human cord-blood lymphocytes or by explants from IM and African BL donors harbor multiple copies of the EBV genome, and viral genetic sequences have also been directly detected in biopsies of African BL. The state of the viral genomes in the carrier cell appears to be such that some are integrated into the cellular DNA while others exist as free, covalently closed circular molecules. (Author Abstract)

184. GENETICS OF ADENOVIRUSES.

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Adv Cancer Res; 23:91-130 1976

The mutagenesis and selection of adenovirus mutants, their use in genetic studies, their phenotypes, and their usefulness in experiments on the regulation of adenovirus replication and cellular transformation are reviewed. Although the adenovirus genome can potentially code for 50 or more proteins, unique mutations have been detected in only 10-12 genes. Of the number of conditionally lethal, temperature-sensitive (ts) mutants isolated, there is considerable clustering of two phenotypes, hexon and assembly mutants. The mutants isolated follow predictive intergenic reactions. The grouping of hexon mutants in a single cistron confirms chemical and physical evidence that the hexon is formed from the assembly of three identical polypeptide chains. Synthesis, assembly, and transport of hexon capsomers require more than a single gene product. The

detection of three nonoverlapping complementation groups representing three genes essential for production of a functional fiber implies that the fiber consists of three rather than two unique species of polypeptides. Types 5 and 12 ts mutants have revealed a minimum of three viral proteins essential for initiation of DNA replication, but only one gene product has been identified so far, a DNA-binding protein that prefers single-stranded DNA. Experiments with two of these mutants, H5ts125 and H5ts149, have confirmed that late transcripts can be made only after replication of viral DNA has begun. The three mutants, H5ts125, H12ts307, and H12ts401, transform significantly more cells than wild-type viruses or other ts mutants. H5ts125 has been most thoroughly characterized and, as previously noted, is defective in a virus-specific, single-stranded DNA-binding protein. The protein of the viral genome that codes for the ts 125 gene product, which is approximately 0.65 physical map unit from the left-hand end of the genome, is rarely integrated in adenovirus-transformed cells. Three independently isolated mutants present this same phenomenon of increased transforming capacity, whereas three other DNA-minus mutants, belonging to another complement group (H5ts36 and 37 and H5ts149), show either decreased or normal transformation frequency. It appears that the adenovirus DNA-binding protein plays a regulatory role in transformation as well as in DNA replication. (140 refs)

185. TUMOR VIRUSES AND CELLULAR GENE EXPRESSION.

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Cancer Res; 36(11):4289-4290 1976

During genetic studies on polyoma virus, a viral gene that appears to act by inducing the expression of certain cellular

genes was identified. Mutants in this viral gene differed in two significant respects from wild-type viruses: they had a restricted host range, and they were unable to induce neoplastic transformation. Isolated originally on polyoma-transformed 3T3 cells as the permissive host, these mutants were subsequently demonstrated to be able to grow as well on type C RNA viral-infected 3T3 cells and on primary mouse embryo fibroblasts. The existence of permissive cells that did not carry integrated polyoma genes suggested that cellular functions were essential for virus replication and that it was the role of the hr-t viral gene to induce the expression of those essential cellular genes. The latter genes were expressed in normal embryo cells and in certain transformed cells, thus displaying features in common with carcinoembryonic antigens. The spontaneous loss of constitutive expression of the cellular permissive factor(s) was apparently counteracted by the action of the hr-t+ viral gene, causing these cellular genes to be reexpressed. Nineteen independent hr-t mutants were isolated. Hr-t mutants were unable to induce a cell surface alteration characteristic of transformed cells, and this could underlie their inability to cause neoplastic transformation. Marker rescue experiments demonstrated that a single wild-type viral DNA restriction enzyme fragment containing approx 13% of the viral genome could restore both a normal host range and transforming ability to the mutants. The hr-t viral gene could act to induce the expression of two classes of cellular genes, those involved in virus replication and those involved in transformation. Histones H-3 and H-4 derived from the wild type showed extensive acetylation compared to normal host cell chromatin, while the same two histone fractions from the hr-t mutant particles demonstrated little increase in acetylation over the host. The hr-t viral function may induce an altered, partially embryonic pattern of cellular gene expression through a process that involves histone modification. (12 Refs)

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